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(54) **Title of the Invention:** Pyrimidine derivative or salt thereof

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(57) **[Abstract]**

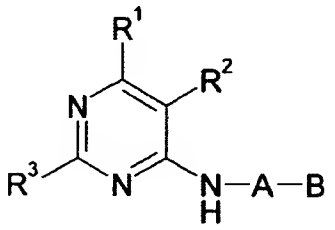
[Problem to Be Solved]

To provide a compound having an excellent effect of promoting insulin secretion and an effect of suppressing blood sugar rise, which can be used in the treatment of insulin-dependent diabetes, non-insulin-dependent diabetes, insulin resistance diseases and obesity.

[Means for Solving the Problems]

The pyrimidine derivative shown in Formula (I) or a pharmaceutically acceptable salt thereof.

[Formula 1]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: -H, -F or methyl.

R^3: an aryl, or aromatic heterocycle, each of which may be substituted.

A: lower alkylene, which may be substituted by one or more –OH.

B: 2-oxopyridyl, which may be substituted and may be condensed with benzene]

[Selected Figure]

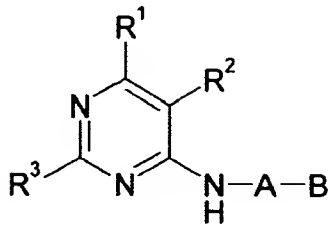
None

[CLAIMS]

[Claim 1]

The pyrimidine derivative shown in Formula (I) or a pharmaceutically acceptable salt thereof.

[Formula 1]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: -H, -F or methyl.

R^3: an aryl, or aromatic heterocycle, each of which may be substituted.

A: lower alkylene, which may be substituted by one or more groups selected from the group consisting of –OH and lower alkyl.

B: 2-oxopyridyl, which may be substituted and may be condensed with benzene]

[Claim 2]

The pyrimidine derivative shown in Formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, with the exception of the following compounds:

3-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-bromophenyl)-5-fluoro-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,3,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-dichlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3-chloro-4-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one, and

4-(2-{[2-(2,3,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one.

[Claim 3]

A pharmaceutical composition having as an active ingredient a compound shown in Formula (I) according to Claim 1.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The present invention relates to a pharmaceutical agent and particularly to a novel pyrimidine derivative, or a pharmaceutically acceptable salt thereof, useful as an agent for promoting insulin secretion or an agent for treating diabetes, and to a medicament having these compounds as an active ingredient thereof.

[0002]

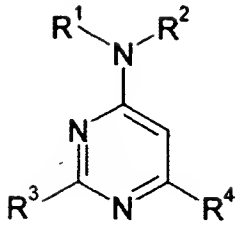
[Prior Art]

Diabetes is a disease primarily characterized by chronic hyperglycemia that develops as a result of relatively or absolutely insufficient insulin action. Clinically, it is broadly divided according to characteristics into insulin-dependent diabetes (hereinafter referred to as "type 1 diabetes") and non-insulin-dependent diabetes (hereinafter referred to as "type 2 diabetes"). One of the major critical causes of type 2 diabetes, which accounts for approximately 90% of diabetics, is decreased insulin secretion from pancreatic β-cells; in particular, postprandial hyperglycemia is observed to result from initial insulin secretion deficiency. Presently, sulphonylurea agents (SU agents) are commonly used as insulin secretion promoters, but these tend to produce hypoglycemia and are known to cause secondary failure due to pancreatic exhaustion in long-term administration. Furthermore, while SU agents are effective for control of blood sugar between meals, suppressing postprandial hyperglycemia is difficult. Recently, large scale clinical trials have confirmed that correction of postprandial hyperglycemia is important in the development of diabetic complications and in controlling progression (Non-Patent Document 1). Furthermore, it has been reported that arterial sclerosis occurs only in the postprandial hyperglycemia period and that persistent mild postprandial hyperglycemia increases death rates due to cardiovascular causes and the like (Non-Patent Document 2). This indicates that, even if mild, postprandial hyperglycemia is an independent risk factor in cardiovascular death. The background described above has resulted in the acknowledgment of the importance and necessity of drug therapies for postprandial hyperglycemia. Accordingly, a pharmaceutical agent having an insulin secretion promoting effect has a profile suitable for correcting postprandial hyperglycemia and/or fasting blood sugar, and may be useful as a therapeutic and prophylactic agent for type 1 diabetes and type 2 diabetes.

[0003]

Meanwhile, pyrimidine derivatives include the compound shown in the following general formula, which is known as an agent used in the treatment of disorders of the circulatory system such as hypertension (Patent Document 1).

[Formula 2]



(See the publication for reference numerals in the formula.)

Note that, in Patent Document 1, diabetes is mentioned as one example of various diseases other than circulatory diseases such as hypertension, but this is not supported by data.

Moreover, in this bulletin, R^4 in the general formula is described in the claims as being a "(C_2-C_5)-alkyl, a trifluoromethyl or an aryl" but specific disclosure in the embodiments is limited to isopropyl, trifluoromethyl, tertiary butyl and phenyl compounds.

[0004]

[Non-Patent Reference 1] *N.Engl. J. Med.*, 329: 977-986, 1993

[Non-Patent Reference 2] *Lancet*, 354:617, 1999, Brit. Med. J., 321: 405-413,2000

[Patent Reference 1] Specification of Unexamined European Patent Application EP-1112266

[0005]

[Problems to Be Solved by the Invention]

As described above, agents for promoting insulin secretion are useful in the treatment and prevention of type 1 diabetes, type 2 diabetes, insulin resistance diseases and obesity; there is therefore a demand for the creation of an agent for promoting insulin secretion having even greater effectiveness.

[0006]

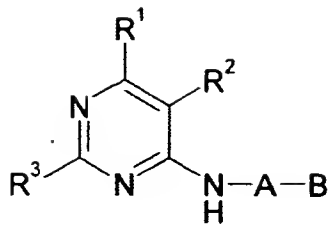
[Means for Solving the Problems]

The present inventors earnestly studied compounds having insulin secretion promotion effects and discovered that a pyrimidine derivative had excellent insulin secretion promotion effects, and thus the present invention was completed.

[0007]

In other words, according to the present invention, the pyrimidine derivative shown in Formula (I), a pharmaceutically acceptable salt thereof, and a pharmaceutical composition having these compounds as an active ingredient, are provided.

[Formula 3]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: H, -F or methyl.

R^3: aryl, or aromatic heterocycle, each of which may be substituted.

A: lower alkylene, which may be substituted by one or more groups selected from the group consisting of –OH and lower alkyl.

B: 2-oxopyridyl, which may be substituted and may be condensed with benzene. Preferably, the pyrimidine derivative shown in Formula (I), or a pharmaceutically acceptable salt thereof, is provided, with the exception of the following compounds.

3-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-bromophenyl)-5-fluoro-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,3,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-dichlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3-chloro-4-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one, and

4-(2-{[2-(2,3,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one.

[0008]

Note that, in Formula (I), R^1 is preferably methyl which may be substituted by one or more halogens, which are the same or different, or ethyl substituted by one or more halogens, which are the same or different, (with the exception of trifluoromethyl), and is more preferably methyl.

Furthermore, in Formula (I) R^2 is preferably –H.

Note that, in Formula (I) R^3 is preferably a phenyl or a pyridyl substituted by one or more halogens, which are the same or different, more preferably a phenyl substituted by 2 to 4 halogens, which are the same or different, and particularly preferably a phenyl substituted by 2 to 4 halogens, which are the same or different, including at least one fluorine.

Furthermore, in Formula (I), A is preferably ethylene, which may be substituted by one or more groups selected from the group consisting of –OH and lower alkyl.

Furthermore, in Formula (I), B is preferably 2-oxopyridyl, which may be substituted by one or more groups selected from the group consisting of lower alkyl, halogen and –OH; more preferably 2-oxopyridine-3-yl, 2-oxopyridine-4-yl or 2-oxopyridine-5-yl, which may be substituted by one or more groups selected from the group consisting of lower alkyl, halogen and –OH.

Furthermore, 2-oxopyridine-4-ylethyl is particularly preferred as –A-B in formula (I).

[0009]

The compound of the present invention shown in Formula (I) is characterized in terms of chemical structure by the fact that the amino group in position 4 of the pyrimidine is substituted by

a 2-oxopyridyl alkyl group and is pharmaceutically characterized by having an effect of promoting insulin secretion.

[0010]

[Modes of Embodiment of the Invention]

The compound represented by Formula (I) is as described hereinafter.

In the definition of the general formulas in the present specification, unless otherwise specified, the term "lower" refers to straight or branched carbon chains, comprising one to six carbon atoms.

Accordingly, the term "lower alkyl" refers to a C_{1-6} alkyl, and specific examples are methyl, ethyl, propyl, butyl, pentyl, or structural isomers thereof, such as hexyl, isopropyl, isobutyl or the like; C_{1-4} alkyls are preferred, and methyl and ethyl are more preferred.

"Lower alkylene" means a C_{1-6} alkylene, and specific examples thereof include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, or hexamethylylene or structural isomers thereof, such as methyl methylene or methyl ethylene, preferably a C_{1-4} alkylene, and more preferably methylene, ethylene and trimethylene.

"Aryl" means a monovalent C_{6-14} aromatic hydrocarbon ring group that is monocyclic to tricyclic, preferably phenyl or naphthyl, and more preferably phenyl. "Aromatic heterocycle" means a monovalent aromatic heterocyclic group, which may be condensed with a benzene ring having one to four identical or different heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur, specifically, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, furazanyl, pyridyl, pyranyl, thiopyranyl, pyridazyl, pyrimidyl, pyrazyl, indolyl, isoindolyl, indolizinyl, benzofuryl, benzothienyl, benzoimidazolyl, indazolyl, benzooxazolyl, benzothiazolyl, benzooxadiazolyl, quinolyl, isoquinolyl, chromenyl, benzothiopyranyl, phthalazinyl, naphthylizinyl, quinoxalinyl, quinoxazolinyl, cinnolinyl, benzodioxolyl, benzodioxinyl, benzodioxepinyl, carbazolyl, or the like; the nitrogen and the sulphur atoms that constitute these rings may be oxidized; in addition, these rings may be partially saturated. Pyridyl, furyl, thienyl, imidazolyl, thiazolyl, oxidopyridyl, pyrazyl, indolyl, benzofuryl, benzothienyl, benzoimidazolyl, benzooxazolyl, benzothiazolyl, benzooxadiazolyl, quinolyl, oxidoquinolyl, isoquinolyl, chromenyl, benzodioxolyl, benzodioxinyl, and benzodioxepinyl are preferred.

"Halogen" includes fluoro-, chloro-, bromo- and iodo-. Fluoro-, chloro- and bromo- are preferred.

[0011]

In the present specification, substituents acceptable [as relates to] the term "which may be substituted" or "substituted" can be any substituent normally used as a substituent for these groups, and may include more than one substituent for each of these groups. Substituents acceptable in terms of "aryl or aromatic heterocycles, which may each be substituted" for R^3, and "2-oxopyridyl, which may be substituted and may be condensed with benzene" for B include the groups cited in (1) to (8) below. Note that "R^{A}" indicates a lower alkyl, which may be substituted by one or more groups selected from the group consisting of -OH, -O-lower alkyl, amino which may be substituted by

one or two lower alkyls, carbonyl which may be substituted by one or two lower alkyls, aryl, an aromatic heterocycle and halogen.

(1) halogen;

(2) -OH, -O-R^A, -O-aryl, -OCO-R^A, oxo(=O);

(3) -SH, -S-R^A, -S-aryl, -SO-R^A, -SO-aryl, -SO_2-R^A, -SO_2-aryl, sulfamoyl, which may be substituted by one or two of R^A;

(4) an amino, which may be substituted by one or two of R^A, -NHCO-R^A, -NHCO-aryl, -$NHCO_2$-R^A, -$NHCONH_2$, -NHCONH-R^A, -$NHSO_2$-R^A, -$NHSO_2$-aryl, nitro;

(5) -CHO, -CO-R^A, -CO_2H, -CO_2-R^A, cyano or carbamoyl, which may be substituted by one or two of R^A;

(6) aryl or cycloalkyl, each of which may be substituted by one or more groups selected from the group consisting of: -OH, -O-lower alkyl, amino, which may be substituted by one or two of R^A, halogen and R^A;

(7) aromatic heterocycle or a non-aromatic heterocycle, which may be substituted by one or more groups selected from the group consisting of: -OH, -O-lower alkyl, amino, which may be substituted by one or two of R^A, halogen and R^A;

(8) lower alkyl, which may be substituted by one or more groups selected from the groups set forth in (1) to (7) above.

Herein, "cycloalkyl" refers to monovalent C_{3-10} carbocyclic groups, and these rings may be crosslinked. Specific examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, norbornyl, and adamanthyl.

The term "non-aromatic heterocycle" means a monovalent non-aromatic heterocyclic group having 1 to 4 heteroatoms chosen from amongst the group consisting of nitrogen, oxygen and sulfur which may be the same or different, and specific examples include: oxetanyl, pyrrolidinyl, tetrahydrofuryl, tetrahydrothiofuryl tetrahydrothiopyranyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperadinyl, morpholinyl, thiomorpholinyl, and quinuclidinyl; the nitrogen and the sulphur atoms that constitute these rings may be oxidized. Pyrrolidinyl, piperidinyl, piperadinyl, and morpholinyl are preferred.

Furthermore, the substituents for "2-oxopyridyl, which may be substituted and may be condensed with benzene" in B, may be substituted at the nitrogen in the pyridyl, which is to say, at position 1 in the 2-oxopyridyl.

[0012]

The compound represented by Formula (I), depending on the type of substituents, may contain an asymmetric carbon atom, and an optically active substance may exist as a result. The present invention includes all the mixtures and isolates of these optical isomers. Furthermore, tautomers may exist for the compound shown in Formula (I), and the present invention includes both separated isomers and mixtures thereof.

In addition, there may be cases where the compounds shown by Formula (I) form salts, which are included in the present invention, as long as such salts are salts that are pharmaceutically acceptable. Specifically, acid addition salts of inorganic acids, such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid and phosphoric acid; organic acids, such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, aspartic acid and glutamic acid; salts of inorganic bases containing metals, such as sodium, potassium, magnesium, calcium and aluminum; salts of organic bases, such as methylamine, ethylamine, ethanolamine, lysine and ornithine; and ammonium salts and the like may be cited.

Furthermore, the present invention also includes substances comprising various hydrates, solvates, or crystal polymorphs of the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention or pharmaceutically acceptable salts thereof. In addition, the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention also includes all compounds that are metabolized *in vivo* and converted into the compounds shown by Formula (I) or the salt thereof, so-called prodrugs. As groups that form prodrugs of the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention, the groups described in *Prog. Med.* 5:2157-2161 (1985) and groups described in "Development of Pharmaceuticals," volume 7, *Molecular Design,* pp. 163-198, Hirokawa Shoten (1990) may be cited.

[0013]

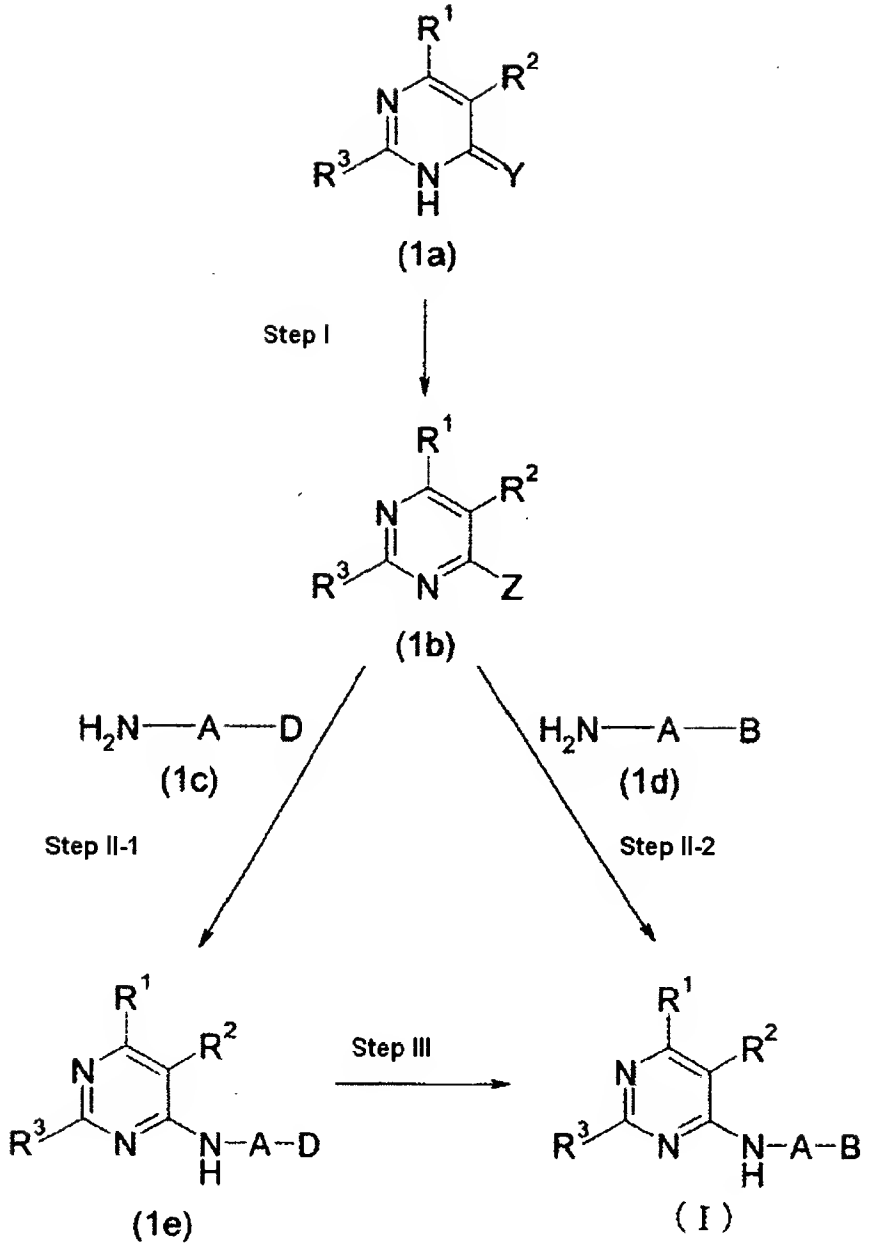
[Manufacturing Method]

The compound shown by Formula (I) or the salt thereof may be manufactured by applying a variety of well-known synthesis methods using characteristics that are based on the basic backbone or the type of substituents. Representative preparations are illustrated below. In addition, depending on the type of functional group, there may be cases where it is effective, in terms of manufacturing technology, to replace, at the raw material or intermediate stage, the functional group in question with a suitably protected group, i.e., a group that can be easily reverted into the functional group in question. Thereafter, the protective group can be eliminated as necessary to obtain the desired compound. For example, such functional groups include the hydroxyl group or the carboxyl group or the amino group, and protective groups therefor include the protective groups described, for instance, in *Protective Groups in Organic Synthesis,* 3rd ed., by Greene and Wuts; these may be used as is suitable according to reaction conditions.

[0014]

Preparation 1

[Formula 4]



(In the scheme, A, B, R^1, R^2 and R^3 have the same meaning as described above; Y indicates O or S; Z indicates a leaving group; and D indicates 2-(lower alkyl-oxy)pyridyl, which may be substituted or condensed with benzene (same hereinafter).)

This preparation is a method in which a pyrimidine derivative, which has a leaving group, shown by Formula (1b), and which can be prepared by halogenation or sulfonylation of the pyrimidinone or pyrimidinethione derivative shown by Formula (1a) according to ordinary methods, is acted upon by an amine having the 2-alkoxypyridyl group or the 2-pyridyl group shown in

Formula (1c) or (1d), and subjected to a dealkylation reaction as necessary, to manufacture the compound of the present invention represented by Formula (I).

The leaving group indicated by Z in Compound (1b) represents a group that can be eliminated in the form of HZ with a hydrogen atom from the amino group of Compound (1c) or (1d) under reaction conditions, and includes, for example, halogens, such as fluoro-, chloro-, bromo-, and iodo-, lower alkylsulfonyloxy groups, such as methanesulfonyloxy, perhalogenomethanesulfonyloxy groups, such as trifluoromethanesulfonyloxy, and arylsulfonyloxy groups, such as benzenesulfonyloxy and p-toluenesulfonyloxy.

Step I

Halogenation in this step is carried out by reacting, for instance, Compound (1a) with a halogenation agent, such as phosphorus oxychloride or phosphorus tribromide. Sulfonylation is carried out by reacting, for instance, Compound (1a) where Y is an oxygen atom and a sulfonylation agent, such as methanesulfonylchloride, p-toluenesulfonylchloride, trifluoromethanesulfonylchloride, or trifluoromethanesulfonic acid anhydride.

Compound (1a) can be prepared by well-known methods, for instance, the methods described in *J. Am. Chem. Soc.*, 74, 842 (1952), *Chem. Ber.*, 95, 937 (1962), or *J. Org. Chem.*, 29, 2887 (1964), or methods based on these methods. Furthermore, compound (1a) is commercially available and can be prepared by well-known methods other than those mentioned above.

Step II-1

In this step, reaction between Compound (1b) and Compound (1c) is carried out at normal pressure or under pressure, without a solvent or in a suitable solvent.

Specific examples of solvents include aromatic hydrocarbons, such as toluene and xylene; ketones, such as methylethylketone and methylisobutylketone; ethers, such as ether, tetrahydrofuran (THF), dioxane, and diglyme; alcohols, such as methanol (MeOH), ethanol (EtOH), and 2-propanol; acetonitrile, dimethylformamide (DMF), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylsulfoxide (DMSO), water, or a solvent that is a mixture of these. It is preferred that this reaction be carried out in the presence of a base. Specific examples of bases include alkaline carbonates, such as sodium carbonate and potassium carbonate; alkaline hydrogen carbonates, such as sodium bicarbonate and potassium hydrogen carbonate; tertiary amines, such as triethylamine and diisopropylethylamine, and the like, and may also be combined with an excess amount of Compound (1c). The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 20°C and approximately 180°C, preferably between approximately 60°C and approximately 130°C.

Step II-2

This step is performed based on Step II-1 of Preparation 1.

Step III

The reaction for dealkylation of the Compound (1e) in this step is carried out at normal pressure or under pressure, without a solvent or in a suitable solvent. Examples of dealkylation

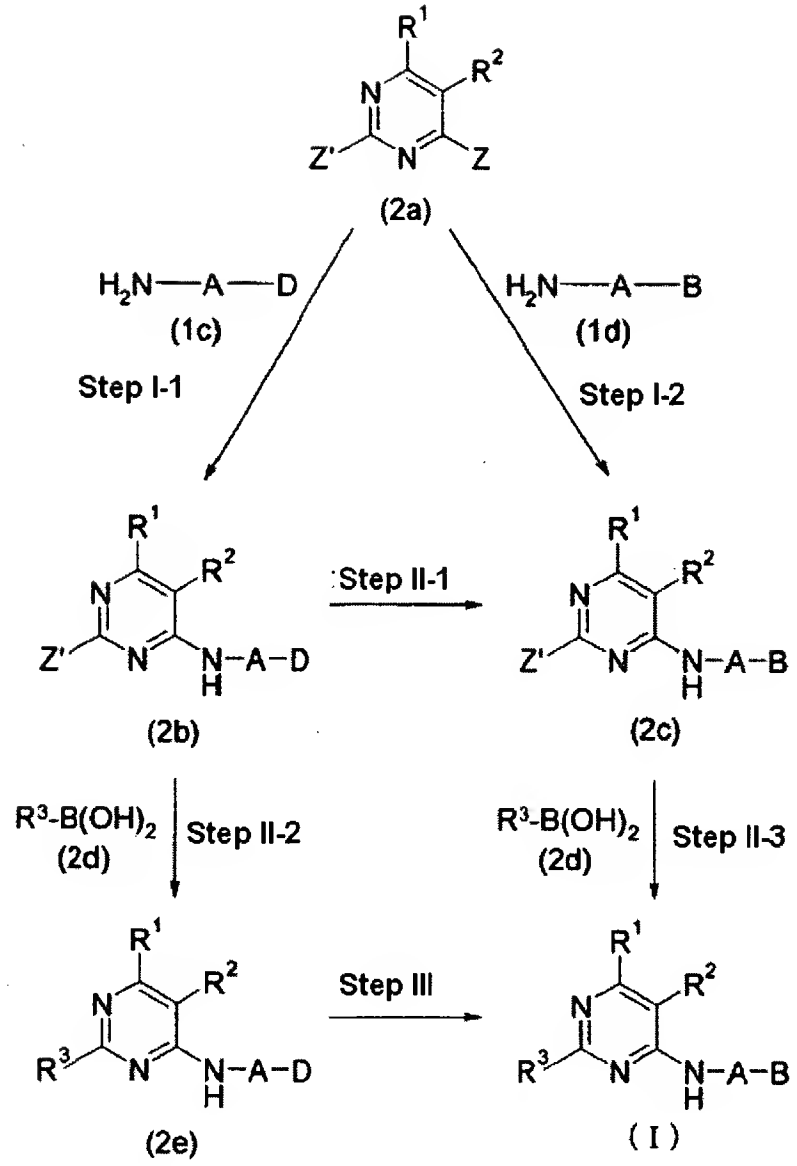
agents used in this reaction include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and phosphoric acid; organic acids such as formic acid, acetic acid and trifluoroacetic acid; Lewis acids such as borontrifluoride etherate complex and aluminum chloride; and iodotrimethylsilane.

Specific examples of solvents include chloroform, ethanethiol, water and mixtures of these solvents, and these can also be combined with an excess amount of acid. The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 0°C and approximately 120°C, preferably between approximately 20°C and approximately 100°C.

[0015]

Preparation 2

[Formula 5]



(In the scheme, Z' indicates the leaving group.)

This preparation is a method in which a pyrimidine derivative having two leaving groups represented by Formula (2a) undergoes the action of an amine having a 2-alkoxypyridine group or a 2-pyridonyl group represented by Formula (1c) or (1d), and is subjected to a dealkylation reaction as necessary, to allow the preparation of a pyrimidine derivative having a leaving group represented by Formula (2b) or (2c), which undergoes the action of the boron derivative represented by Formula (2d), and is subjected to a dealkylation reaction as necessary, to manufacture the compound of the present invention shown by the Formula (I).

The leaving group indicated by Z' in Compounds (2a), (2b) and (2c) is the same as the leaving group indicated by Z in Compound (1b) shown in Preparation 1, and Z and Z' may be the same or different.

Step I-1 and Step I-2

These steps are performed based on Step II-1 and Step II-2 of Preparation 1.

Step II-1 and Step III

These steps are performed based on Step III in Preparation 1.

Step II-2 and Step II-3

The condensation reactions in these steps are carried out at normal pressure or under pressure, without a solvent or in a suitable solvent.

Specific examples of solvents include aromatic hydrocarbons, ketones, ethers, alcohols, acetonitrile, DMF, DMSO, water, or a solvent that is a mixture thereof. It is preferred that the present reaction be carried out in the presence of a base, and specific examples of bases include alkaline carbonates, alkaline hydrogen carbonates, tertiary amines, and the like. The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 20°C and approximately 180°C, preferably between approximately 60°C and approximately 130°C.

Furthermore, this reaction may advance smoothly as a result of adding transition metals or transition metal-phosphine complexes. Specific examples thereof include palladium-carrying carbon, dichloro[1,4-bis(diphenylphosphine)butane]palladium, tetrakis(triphenylphosphine)palladium, and the like; those described in specific examples in U.S. Patent Publication No. 5550236 can also be used.

[0016]

Furthermore, some compounds shown by Formula (I) can also be prepared from compounds obtained in the manner described above, by combining any processes conventionally used by those skilled in the art, such as well-known alkylation, acylation, oxidation, and reduction.

[0017]

The compound of the present invention manufactured in this way is isolated/purified, either in free form or as a salt thereof, using ordinary salt formation processes. Isolation/purification is carried out by applying ordinary chemical operations, such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, precipitation, and various chromatographies.

Various isomers can be isolated by ordinary methods, using the differences in physicochemical properties between the isomers. For instance, racemic mixtures can be used to produce an optically pure isomer by common separation methods for racemic bodies, such as, for instance, a method in which a diastereomeric salt is produced with a generic optically active acid, such as tartaric acid, and resolved optically. In addition, diastereo mixtures can be separated, for instance, by fractional crystallization or various chromatographies. In addition, optically active compounds can be manufactured by using raw materials with suitable optical activity.

[0018]

[Effects of the Invention]

The compound of the present invention as indicated by Formula (I) has an excellent effect of promoting insulin secretion and an effect of suppressing blood sugar rise. Consequently, based on these effects, the compound shown by Formula (I) is useful in the treatment and/or prophylaxis of type 1 diabetes, type 2 diabetes, insulin resistance diseases, and/or obesity.

[0019]

The pharmacological effects of the compound of the present invention have been verified by the following test methods.

(1) Test for measuring the effect of promoting insulin secretion

In this test, the effect of promoting insulin secretion was examined for the test compound using MIN6 cells or MIN6B1 cells, which are mouse pancreatic β cell strains. The test method is described below.

MIN6 cells or MIN6B1 cells were sown in a 24-well plate so as to obtain 2 x 10^5 cells/well (0.4 ml) (culture medium used was DMEM containing 25 mM glucose to which FCS was added to 10%). After 2 days, the culture medium was removed with an aspirator, washed once with 1 ml of KRB-HEPES (140 mM NaCl, 3.6 mM KCl, 0.5 mM NaH2PO4, 0.5 mM $MgSO_4$, 1.5 mM $CaCl_2$, 2 mM $NaHCO_3$, 0.1% BSA, and 10 mM HEPES (pH 7.4)) containing 2.8 mM glucose warmed to 37°C; 1 ml of the same buffer solution was introduced again and incubated for between 30 minutes and 60 minutes at 37°C. The buffer solution was removed with an aspirator; 0.5 ml of each of KRB-HEPES containing 16.8 mM glucose to which 10 μM each of test compound had been added was added to each well and incubated for 22 minutes at 37°C. The samples were fractionated, and 2.0 μl to 2.5 μl were diluted in 50 μl of PBS; insulin concentration was determined using the Phadeseph insulin RIA kit (manufactured by Pharmacia, Upjohn) or a rat insulin [^{125}I] assay system RPA549 (Amersham Biosciences). The test compound was dissolved in 100% DMSO and added at a final concentration of 0.1%. The activity was expressed as a relative ratio where DMSO is 100%. The results are shown in Table 1.

Note that, in the description of the compounds in the table, "Ex" indicates the example number of the example compound described below (same hereinafter).

[0020]

[Table 1]

Compound	Insulin secretion promoting effect (%)
Ex 5	206
Ex 9	153
Ex 18	148
Glibenclamide	122

As described above, the compound of the present invention showed a strong effect of promoting insulin secretion.

[0021]

[*sic Paragraph 0021 in the original Japanese publication contains no text. – trans.*]

[0022]

(2) Test by oral sugar loading with normal mouse

In this test, the activity of the test compound in terms of suppressing blood sugar rise after sugar loading was examined using a normal mouse. The test method is described below.

An ICR mouse (male, 6 weeks old), prebred for 1 week, was fasted for 18 to 20 hours and used as test animal. The test compound was dissolved in water and administered orally at 3 mg/kg (10 mg/kg for Nateglinide) 5 minutes prior to glucose load (30 minutes before for Nateglinide). The rate of blood sugar decrease (%) versus the control group 30 minutes after glucose loading was measured. The results are shown in Table 2.

[0023]

[Table 2]

Compound	Rate of blood sugar decrease (%)
Ex 14	25
Nateglinide	26

As described above, the compound of the present invention showed a strong blood sugar lowering effect in the oral sugar loading test with the normal mouse.

[0024]

The pharmaceutical agent of the present invention can be prepared by methods used conventionally, using one or more of the compounds indicated by Formula (I) and an agent carrier, an excipient, and other additive agents used in conventional formulation. Administration may be in any form, including oral administration of tablets, pills, capsules, granules, powders, subtle granules, solutions, and the like; parenteral administration, such as via injectables, such as intravenous injection and intramuscular injection; or suppository, nasotracheal, transmucosal, percutaneous, and the like.

Tablets, powders, granules, and the like can be used as solid compositions for oral administration of the present invention. In such solid compositions, one or more active substance is mixed with at least one inert diluent, such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium aluminate metasilicate, or the like. According to methods of the art, the composition may contain an additive agent in addition to the inert diluent, for instance, a lubricant, such as magnesium stearate; a disintegrant, such as fibrous calcium gluconate; a stabilization agent, such as lactose; a solubilizer, such as glutamic acid or aspartic acid; or a dissolution adjuvant. Tablets or pills may be coated as necessary with a

sugar coating, such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, or a film soluble in the stomach or intestine.

[0025]

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, and the like, and includes commonly used inert diluents, such as purified water and EtOH. Such compositions may contain, in addition to the inert diluent, adjuvants, such as a solubilizer, a dissolution adjuvant, a wetting agent, a suspensioning agent, as well as sweetening agents, flavoring agents, aroma agents, and preservatives.

Injectables for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Diluents for aqueous solutions and suspensions include, for instance, distilled water and physiological saline for injectables. As diluents for non-aqueous soluble solutions and suspensions, for instance, propyleneglycol, polyethyleneglycol, plant oils, such as olive oil, alcohols, such as EtOH, and Polysorbate 80 (product name) are available. Such compositions may further contain additive agents, such as an isotonization agent, preservatives, a wetting agent, an emulsifying agent, a dispersant, a stabilization agent, such as, for instance, lactose, a solubilizer, or a dissolution adjuvant. These are sterilized by, for instance, filtration in which this is passed through a bacteria-retaining filter, mixing this with bactericide, or bombardment. These may also be used by producing them as sterile solid compositions and dissolving these in sterile water or a sterile injectable solvent prior to use.

In case of conventional oral administration, a daily dose of 0.1 to 500 mg per adult is adequate, and this is administered once or separated into two to four doses. In case of intravenous administration, a daily dose of 0.01 to 100 mg per adult is adequate, and this is administered once or separated into two to four doses. The dose is determined optimally according to each case considering the symptoms, age, body weight, sex, and the like. Since the dose varies due to a variety of factors, an amount less than the administration range described above may be sufficient.

[0026]

[Examples]

The present invention will be described below by way of examples; however, the present invention is not limited in any way by these examples. In addition, the raw material compounds used in the examples also contain novel substances, and description will be given using the preparation of such raw material compounds from well-known compounds as reference examples.

[0027]

Reference Example 1

After stirring a mixture of 31.32 g of 4-bromo-2,5-diflurobenzoic acid, 100 ml of thionyl chloride and 0.5 ml of DMF for 2 hours at 80°C, 200 ml of toluene was added and the solvent was evaporated *in vacuo*. 200 ml of chloroform was added to the residue and 200 ml of 28% ammonia water was instilled in ice and this was stirred for 1 hour at the same temperature. The reaction solution was extracted with chloroform, and after washing the organic layer with a saturated saline

solution (brine), this was dried with anhydrous magnesium sulfate (M_GSO_4). The solvent was evaporated *in vacuo* to produce 28.42 g of 4-bromo-2,5-difluorobenzamide as a light yellow solid.

The compound of Reference Example 2 was produced in the same manner as Reference Example 1.

[0028]

Reference Example 3

A mixture of 28.37 g of 4-bromo-2,5-difluorobenzamide and 115 ml of phosphorus oxychloride was stirred for 1.5 hours at 80°C, whereafter 250 ml of toluene was added and the solvent was evaporated *in vacuo*. 300 ml of ice water was added to the residue, and after extraction with ether, the organic layer was washed with saturated aqueous sodium bicarbonate and brine, followed by drying with M_GSO_4. The solvent was evaporated *in vacuo* to produce 26.82 g of 4-bromo-2,5-difluorobenzonitrile as a yellow solid.

The compound of Reference Example 4 was produced in the same manner as Reference Example 3.

[0029]

Reference Example 5

Hydrochloric acid gas was blown for 30 minutes at –65°C into a mixture of 18.20 g of 4-bromobenzonitrile, 300 ml of chloroform, and 100 ml of EtOH while stirring, which was subsequently stirred overnight at room temperature. After evaporating the solvent *in vacuo*, 48 g of ammonium carbonate and 400 ml of EtOH were added to the residue and stirred for 3 days at room temperature. After adding 300 ml of water to the reaction solution, EtOH was evaporated *in vacuo*, and the deposited solids were collected by filtration, rinsed, and 22.91 g of 4-bromobenzamidine hydrochloride was obtained as colorless solids.

The compounds of Reference Examples 6 to 9 were obtained in the same way as in Reference Example 5.

[0030]

Reference Example 10

9.72 g of sodium methoxide was added to 250 ml MeOH solution of 14.13 g of 4-bromobenzamidine hydrochloride, and after stirring for 30 minutes at room temperature, 7.50 ml of methyl acetoacetate was added, and this was stirred for 20 hours at 60°C. To the reaction solution, 400 ml of aqueous solution of 1 M HCl was added under ice-cold conditions, the deposited solids were collected by filtration, rinsed, and 13.98 g of 2-(4-bromophenyl)-6-methyl-3H-pyrimidine-4-one was obtained as colorless solids.

The compounds of Reference Examples 11 to 15 were obtained in the same way as in Reference Example 10.

[0031]

Reference Example 16

A mixture of 8.80 g of 2-(4-bromophenyl)-6-methyl-3H-pyrimidine-4-one and 80 ml of phosphorus oxychloride was stirred for 2 hours at 80°C. After the solvent was evaporated *in vacuo*, 100 ml of ice water and 150 ml of an aqueous solution of 1 M NaOH were added successively to the residue, the deposited solids were collected by filtration, rinsed, and 10.13 g of 2-(4-bromophenyl)-4-chloro-6-methylpyrimidine was obtained as colorless solids.

The compounds of Reference Examples 17 to 21 were obtained in the same way as in Reference Example 16.

[0032]

The structures and the physical data for the Reference Example compounds are shown in Tables 3 to 5. Note that the notations in the table have the following meanings (same hereinafter):

Rf: Reference Example number

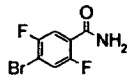
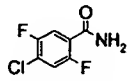
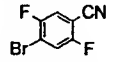
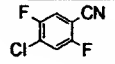
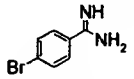
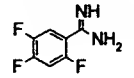
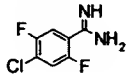
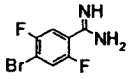
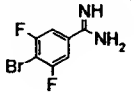
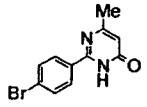
Data: Physical data, FMS: mass spectrometric data (if not otherwise specified, FAB-MS$(M+H)^+$ data), NMR: NMR data ($(CH_3)_4Si$ serves as the internal reference, and if not otherwise specified, δ (ppm) of the peak in ^{1}H-NMR with DMSO-d_6 as the measurement solvent)

Salt: salt (HCl: hydrochloride, HBr: hydrobromic acid salt, fum: fumarate, Ox: oxalate, unless otherwise specified: free-body)

Structure: chemical structure formula, Me: methyl, Et: ethyl.

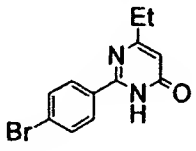
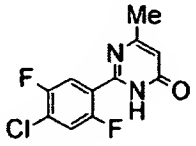
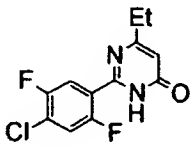
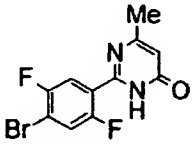
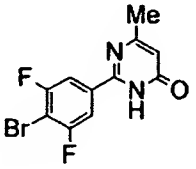
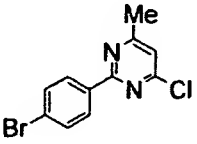
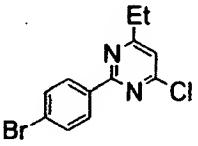
[0033]

[Table 3]

Rf (Salt)	Structure	Data
1		FMS:236,238.
2		FMS:192.
3		EI-MS(M^+):217,219.
4		EI-MS(M^+):173.
5 (HCl)		FMS:199,201.
6		FMS:175.
7		FMS:191.
8		EI-MS(M^+):234,236.
9		FMS:237.
10		FMS:265,267.

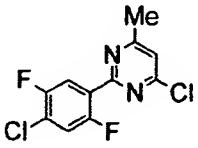
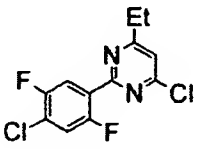
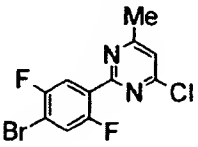
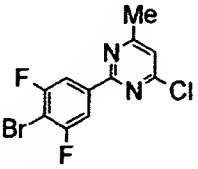
[0034]

[Table 4]

Rf (Salt)	Structure	Data
11		FMS:279,281.
12		FMS:257.
13		FMS:271.
14		FMS:301,303.
15		FMS:301,303.
16		FMS:285.
17		FMS:299.

[0035]

[Table 5]

Rf (Salt)	Structure	Data
18		FMS:275.
19		FMS:289.
20		FMS:321.
21		FMS:319,321.

[0036]

Reference Example 22

An amount of a 200 ml THF solution of 19.06 g of methyl 2-methoxyisonicotinate was added to a mixture of 4.33 g of lithium aluminium hydride and 340 ml of THF under ice-cold conditions and stirred for 1 hour at the same temperature.

Under ice-cold conditions, 70 ml of aqueous THF (1:1) were added to the reaction liquid and, after filtering over Celite, the solvent was evaporated *in vacuo* to produce 16.96 g of (2-methoxypyridine-4-yl)methanol as an oily, orange-colored substance.

FAB-MS$(M+H)^+$:140.

[0037]

Reference Example 23

After instilling 89 ml of thionyl chloride into 16.96 g of (2-methoxypyridine- 4-yl)methanol under ice-cold conditions, this was stirred for 2.5 hours at the same temperature, and then stirred for a further 4 hours at room temperature. After evaporating the solvent *in vacuo*, the saturated aqueous solution of sodium bicarbonate was added to the residue and this was extracted with chloroform.

The organic layer was dried with $MgSO_4$, whereafter the solvent was evaporated *in vacuo* to produce 15.06 g of 4-(chloromethyl)-2-methoxypyridine as an oily brown substance.

FAB-MS$(M+H)^+$:158.

[0038]

Reference Example 24

A mixture of 15.06g of 4-(chloromethyl)-2-methoxypyridine, 12.44 g of potassium cyanide, 25.26 g of 18-crown-6-ether and 300 ml of acetonitrile was stirred for 12 hours at room temperature. After evaporating the solvent *in vacuo*, 400 ml of water was added to the residue and this was extracted with ethyl acetate (EtOAc). After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 9.51 g of (2-methoxypyridine-4-yl) acetonitrile as a yellow solid.

FAB-MS$(M+H)^+$:149.

[0039]

Reference Example 25

Raney nickel (suspension) was added to a solution of 9.51 g of (2- methoxypyridine-4-yl) acetonitrile in 100 ml of EtOH and 25 ml of ammonia water, under hydrogen atmosphere, and stirred for 8 hours at room temperature. After the reaction solution was filtered over Celite, the solvent was evaporated *in vacuo*, and 9.06 g of 3-(2-aminoethyl)-2-methyl pyridine was obtained as an oily, brown substance.

FAB-MS$(M+H)^+$:153.

[0040]

Reference Example 26

A mixture of 15.0 g (6-methoxypyridine-3-yl)methanol, 228 g of magnesium dioxide and 400 ml of acetone was stirred for two days at room temperature. After filtering the reaction solution and evaporating the solvent *in vacuo*, the deposited solids were collected by filtration and washed with hexane to produce 7.05 g of 6-methoxynicotine aldehyde as colorless solids.

FAB-MS$(M+H)^+$:138.

[0041]

Reference Example 27

2.83 g of a 60% oil suspension of sodium hydride was added to a 100 ml THF solution of 11.6 of triethyl phosphonoacetate under ice-cold conditions, and this was stirred for 10 minutes at the same temperature, whereafter a 50 ml THF solution of 5.92 g of 6-methoxynicotine aldehyde was added and this was stirred at room temperature for 2 hours.

Ice water was added to the solution and this was extracted with EtOAc, whereafter the organic layer was washed with saturated saline and dried with $MgSO_4$.

After evaporating the solvent *in vacuo*, the residue was purified by silica gel column chromatography (hexane : EtOAc) to produce 7.52 g of ethyl (2E)-3-(6-methoxypyridine-3-yl) acrylate as a colorless oily substance.

FAB-MS(M+H)$^+$:208.

[0042]

Reference Example 28

750 mg of 10% palladium-carrying carbon was added to a 100 ml EtOH solution of 7.50 g of ethyl (2E)-3-(6-methoxypyridine-3-yl) acrylate, and this was stirred for 2 hours at room temperature in a hydrogen atmosphere. After the reaction solution was filtered over Celite, the solvent was evaporated *in vacuo*, and 7.57 g of ethyl 3-(6-methoxypyridine-3-yl)propionate was obtained as colorless oily substance.

FAB-MS(M+H)$^+$:210.

[0043]

Reference Example 29

38.1 ml of n-butyllithium (1.5 M hexane solution) was instilled into a 100 ml THF solution of 5.86 g of 2-methoxy-6-methylpyrimidine, whereafter 7.94 g of paraformaldehyde was added, and this was stirred overnight at room temperature. Ice water was added to the reaction solution and this was extracted with EtOAc, whereafter the organic layer was washed with brine and dried with $MgSO_4$. After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 1.68 g of 2-(6-methoxypyridine- 2-yl)ethanol as a colorless oily substance.

NMR:2.79(2H,t),3.72-3.76(2H,m),3.82(3H,s),4.59(1H,t),6.61(1H,d),6.83(1H,d),7.56-7.62(1H,m).

[0044]

Reference Example 30

A mixture of 2.05 g of 5-(chloromethyl)-2-methoxypyridine, 2.65 g of phthalimide potassium and 20 ml of DMF was stirred for two hours at 100°C. Ice water was added to the reaction solution, and the deposited solids were collected by filtration and washed to produce 1.91 g of 2-[(6-methoxypyridine-3-yl)methyl]-1H-isoindol- 1,3(2H)-dione as colorless solids.

FAB-MS(M+H)$^+$:269.

[0045]

Reference Example 31

A mixture of 1.91 g of 2-[(6-methoxypyridine-3-yl)methyl]-1H-isoindol-1,3(2H)-dione, 1.7 ml of hydrazine hydrate and 20 ml of MeOH was stirred overnight at room temperature, whereafter the reaction solution was filtered and the solvent was evaporated. 30 ml of 1M aqueous NaOH was added to the residue and this was extracted with chloroform. The organic layer was washed with brine and dried with $MgSO_4$, whereafter the solvent was evaporated *in vacuo* to produce 700 mg of [(6-methoxypyridine-3-yl)methyl]amine.

FAB-MS(M+H)$^+$:139.

[0046]

Reference Example 32

To a 200 ml DMF solution of 10.7 g of 2-methoxyisonicotinic acid were successively added under ice-cold conditions 10.4 g of 1-hydroxybenzotriazole, 14.8 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 7.51 g of N,O-dimethylhydroxylamine hydrochloride and 21.4 ml of trimethylamine, and this was stirred at room temperature for 20 hours. After evaporating the solvent *in vacuo*, water was added and this was extracted with EtOAc. After washing the organic layer with saturated aqueous sodium bicarbonate and drying with $MgSO_4$, the solvent was evaporated *in vacuo*. The residue was purified by silicone gel chromatography (chloroform : MeOH : ammonia water) to produce 13.4 g of N,2-dimethoxy-N-methylisonicotinamide.

FAB-MS$(M+H)^+$:197.

[0047]

Reference Example 33

22.3 ml of a 1.2 M methyllithium ether solution was instilled into a 100 ml THF solution of 5.0 g of N,2-dimethoxy-N-methylisonicotinamide at 78°C, whereafter this was warmed to room temperature while stirring. Water was added to the reaction solution, and after evaporating the solvent *in vacuo*, brine was added to the residue and this was extracted with EtOAc. After drying the organic layer with $MgSO_4$ and evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (hexane : EtOAc) to produce 3.17 g of 1-(2-methoxypyridine-4-yl)ethanone.

EI-MS(M^-):150.

[0048]

Reference Example 34

To a 50 ml DME solution of 1.60 g of 1-(2-methoxypyridine-4-yl)ethanone were successively added at –15°C, 2.17 g of tosylmethyl isocyanide, 2.5 g of butoxypotassium and 5 ml of EtOH, and this was stirred for 3 hours while gradually warming it to room temperature. After evaporating the solvent *in vacuo*, water was added to the residue and this was extracted with ether. After drying the organic layer with $MgSO_4$ and evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (hexane : EtOAc) to produce 3.17 g of 1-(2-methoxypyridine-4-yl)ethanone.

EI-MS(M^-):161.

[0049]

Reference Example 35

A mixture of 1.35 g of 2-methoxyisonicotinenicotine aldehyde, 7.51 g of N,O-dimethylhydroxylamine hydrochloride, 1.63 g of potassium carbonate and 10 ml of EtOH was stirred for 30 minutes at room temperature. After filtering the reaction solution over Celite and evaporating the solvent *in vacuo*, 500 mg of 10% palladium-carrier carbon was added to the residue and this was stirred for 22 hours under a hydrogen atmosphere. After filtering the reaction solution over Celite and evaporating the solvent *in vacuo*, a saturated aqueous solution of sodium bicarbonate was added to the residue and this was extracted with chloroform. After drying the organic layer with $MgSO_4$ and evaporating the solvent *in vacuo*, the residue was purified by silica

gel chromatography (hexane : MeOH : aqueous ammonia) to produce 415 mg of [(2-methoxypyridine-4-yl)methyl]amine.

FAB-MS(M+H)$^+$:139.

[0050]

Reference Example 36

2.05 ml of diethyl cyanomethylphosphonate was added to a 30 ml THF solution of 0.48 of a 60% sodium hydride oil suspension, under ice-cold conditions, and stirred for 30 minutes at the same temperature, whereafter a 20 ml THF solution of 1.50 g of 2-methoxyisonicotine aldehyde was added, and this was stirred for 15 hours at room temperature. Water was added to the residue produced by evaporating the solvent *in vacuo* and this was extracted with EtOH, whereafter the organic layer was washed with brine and dried with $MgSO_4$. After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 1.14 g of 3-(2-methoxypyridine-4-yl) acrylonitrile as colorless solids.

FAB-MS(M+H)$^+$:161.

[0051]

Reference Example 37

2.56 g of sodium cyanide and 8.51 g of diethyl cyanophosphonate were added to an 80 ml THF solution of 2.38 g of 2-methoxyisonicotine aldehyde, and this was stirred for 30 minutes at the same temperature. Water was added to the residue produced by evaporating the solvent *in vacuo* and this was extracted with EtOH, whereafter the organic layer was washed with water and saturated saline and dried with $MgSO_{44}$. After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 2.22 g of diethyl cyano(2- methoxypyridine-4-yl) methylphosphonate.

FAB-MS(M+H)$^+$:301.

[0052]

Reference Example 38

A 100 ml THF solution of 2.21 g of diethyl cyano(2-methoxypyridine-4-yl)methylphosphonate was instilled into a 100 ml THF suspension of 0.84 g of lithium aluminum hydride, under ice-cold conditions, and this was stirred for 20 hours at room temperature.

To the reaction solution were successively added, under ice-cold conditions, 0.84 ml of water and 0.84 ml of a 15% aqueous NaOH solution, and after stirring for 30 minutes, a further 2.52 ml of water was added and this was stirred for 2 hours at room temperature. After filtering the reaction solution over Celite and evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (chloroform : MeOH : ammonia water) to produce 510 mg of 2-amino-1-(2-methoxypyridine-4-yl)ethanol.

FAB-MS(M+H)$^+$:169.

[0053]

Reference Example 39

28 ml of a 1.0 M borane-THF complex was added to a 50 ml THF solution of 1.70 g of (2-chloro-6-methoxypyridine-4-yl)acetonitrile under ice cold conditions, and this was stirred for 2 hours at room temperature and for an additional one hour with hot reflux. After cooling the reaction solution, 10 ml of methanol and 12 ml of 6 M hydrochloric acid were successively added, and this was stirred for 30 minutes at room temperature and for an additional 1 hour under heat reflux. A 2M aqueous solution of NaOH was added to the residue produced by evaporating the solvent *in vacuo*, and after extracting this with chloroform, the organic layer was dried with $MgSO_4$. After evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (chloroform : MeOH : ammonia water) to produce 740 mg of [2-(2-chloro-6-methoxypyridine-4-yl)ethyl]amine.

FAB-MS$(M+H)^+$:187.

[0054]

Reference Example 40

A mixture of 210 mg of 2-(4-bromo-2,5-diflurophenyl)-4-chloro-6-methylpyrimidine, 200 mg of [2-(2-methoxypyridine-4-yl)ethyl]amine, 454 mg of potassium carbonate and 2 ml of DMI was stirred overnight at 95°C. Water was added to the reaction solution and extracted with toluene, whereafter the organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo* to produce 304 mg of [2-(4-bromo-2,5-diflurophenyl)-6-methylpyrimidine-4-yl][2-(2-methoxy-4-pyridyl)ethyl]amine as an oily yellow substance.

FAB-MS$(M+H)^+$:435,437.

[0055]

Working Example 1

A mixture of 304 mg of [2-(4-bromo-2,5-diflurophenyl)-6-methylpyrimidine-4-yl] [2-(2-methoxy-4-pyridyl)ethyl] amine and 3.0 ml of 48% aqueous hydrogen bromide was stirred overnight at 80°C. A saturated aqueous solution of sodium bicarbonate was added to the reaction solution, and this was extracted with EtOAc, and after washing the organic layer with a 1M aqueous NaOH solution, this was dried with $MgSO_4$. Ether was added to a residue that was produced by evaporating the solvent *in vacuo*, and the deposited solids were collected by filtration to produce 163 mg of 4-(2-{[2-(4-bromo-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one as colorless solids.

[0056]

Working Example 2

0.122 ml of dimethyl sulfate and 1 ml of DMF were added to a mixture of 235 mg of 4-(2-{[2-(4-bromo-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one hydrochloride and 4 ml of a 1M NaOH aqueous solution. After stirring the reaction mixture overnight at room temperature, water was added and the mixture was extracted with ethyl acetate. After washing the organic layer with the saturated aqueous solution of sodium bicarbonate, this

was dried with $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to produce a white solid. 10 ml of chloroform-MeOH and 4 ml of a 4M HCl-dioxane solution were added to the substance and this was concentrated *in vacuo.* The residue was crystallized with EtOH-MeOH to produce 180 mg of 4-(2-{[2-(4-chloro-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)-1-methylpyrimidine-2(1H)-one hydrochloride.

[0057]

Working Example 3

A mixture of 815 mg of 2-(4-bromo-2,5-difluorophenyl)-6-chloro-4-methylpyrimidine, 480 mg of 4-(2-ethylamino)-2(1H)-quinolinone, 3.25 ml of diisopropylethylamine and 20 ml of acetonitrile was stirred overnight at 80°C. The reaction mixture was concentrated *in vacuo* and the residue was purified with silica gel chromatography (chloroform-MeOH) to produce a solid. 1 ml of a 4M dioxane solution of hydrochloric acid was added to this solid in 10 ml of chloroform-MeOH, and this was concentrated *in vacuo* to produce a solid. This solid was washed with ether to produce 260 mg of 4-(2-{[2-(4-bromo-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl) quinolinone-2(1H)-one hydrochloride.

[0058]

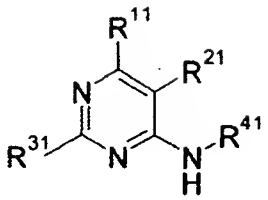
The structures and physical data for the exemplary compounds described above are shown in Table 6. Furthermore, the structures and physical data for exemplary compounds produced by the same preparation methods as used for these exemplary compounds are shown in Tables 6 to 10. Note that, in the tables, the notations have the following meanings.

Ex: Example No.

R^{11}, R^{21}, R^{31} and R^{41}: Substituents in the general formulas (Ph: phenyl, PyO: 2-oxopyridyl, QuiO: 2-oxoquinolinone, di: di, tri: tri). The numerals preceding the substituent denote the site of substitution. Accordingly, for example, 4-Br-2,5-diF-Ph indicates 4-bromo-2,5-difluorophenyl, $-(CH_2)_2$-(1-Me-5-PyO) indicates 1-methyl-2-oxopyridine-5-ylethyl and $-(CH_2)_2$-(4-QuiO) indicates 2-oxo oxoquinolinone -4- ylethyl.)

[0059]

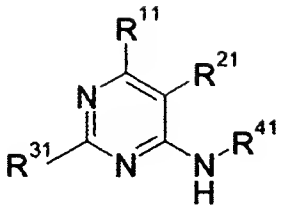
[Table 6]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
1	R^{11} : Me R^{21} : -H R^{31} : 4-Br-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.27(3H,s),2.68(2H,t),3.40-3.60(2H,br),6.09(1H,d),6.15(1H,s),6.31(1H,s),7.26(1H,d),7.40-7.60(1H,br),7.78(1H,dd),7.82-7.91(1H,m),11.3-11.4(1H,br) FMS:421.
2 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Cl-2,5-diF-Ph R^{41} : -$(CH_2)_2$-(1-Me-4-PyO)	NMR:2.45(3H,s),2.74(2H,t),3.37(3H,s),3.60-3.80(2H,m),6.17(1H,d),6.26(1H,s),6.66(1H,s),7.61(1H,d),7.96-8.08(2H,m),9.70(1H,s). FMS:391.
3 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Br-2,5-diF-Ph R^{41} : -$(CH_2)_2$-(4-QuiO)	NMR:2.45(3H,s),3.05-3.20(2H,m),3.75-3.85(2H,m),6.39(1H,s),6.66(1H,m),7.07(1H,t),7.25(1H,d),7.44(1H,t),7.79(1H,dd),7.86(1H,d),8.06(1H,dd),9.69(1H,brs),11.63(1H,brs). FMS:471.
4 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-5-PyO	NMR:2.45(3H,s),2.69(2H,t),3.73(2H,q),6.35(1H,d),6.57(1H,s),7.30-7.36(1H,m),7.50(1H,dd),7.90(2H,d),8.12(2H,d),9.35(1H,s). FMS:385,387.
5 (Ox)	R^{11} : Et R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-5-PyO	NMR:1.21(3H,t),2.52-2.64(4H,m),3.30-3.70(2H,m),6.28(1H,d),6.28(1H,s),7.18(1H,s),7.41(1H,dd),7.42-7.50(1H,m),7.67(2H,d),8.25(2H,d). FMS:399,401.
6 (Ox)	R^{11} : Et R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-(1-Me-5-PyO)	NMR:1.21(3H,t),2.52-2.64(4H,m),3.37(3H,s),3.40-3.70(2H,m),6.29(1H,s),6.34(1H,d),7.39(1H,dd),7.42-7.55(2H,m),7.67(2H,d),8.25(2H,d). FMS:413,415.

[0060]

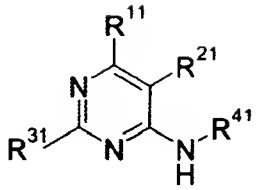
[Table 7]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
7	R^{11} : Et R^{21} : -H R^{31} : 3-Cl-4-F-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:1.22(3H,t),2.58(2H,q),2.72(2H,t),3.40-3.80(2H,br),6.15(1H,dd),6.20(1H,s),6.30(1H,s),7.28(1H,d),7.51(1H,dd),7.40-7.65(1H,br),8.25-8.37(1H,m),8.42(1H,dd). FMS:373.
8	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.26(3H,s),2.68(2H,t),3.30-3.70(2H,br), 6.09(1H,d),6.15(1H,s),6.30(1H,s),7.26(1H,d),7.40-7.55(1H,br),7.55-7.65(1H,m),7.70-8.00(1H,m),11.3-11.4(1H,br) FMS:361.
9	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-5-PyO	NMR:2.26(3H,s),2.58(2H,t),3.40-3.60(2H,m),6.26(1H,d),6.58(1H,brs),7.16(1H,brs),7.37(1H,d),7.46(1H,brs),7.55-7.64(1H,m),7.85-8.00(1H,m),11.39(1H,brs). FMS:361.
10	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -(CH_2)-5-PyO	NMR:2.27(3H,s),4.29(2H,brs),6.31(1H,d),6.34(1H,brs),7.31(1H,s),7.43(1H,dd),7.59(1H,dt),7.75(1H,t),7.90-8.02(1H,m),11.43(1H,brs). FMS:347.
11	R^{11} : Me R^{21} : -H R^{31} : 4-Br-3-F-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.28(3H,s),2.70(2H,t),3.50-3.80(2H,br),6.12(1H,dd),6.18(1H,s),6.30(1H,s),7.27(1H,d),7.36-7.52(1H,br),7.80(1H,dd),8.00-8.02(2H,m),11.1-11.5(1H br) FMS:403.

[0061]

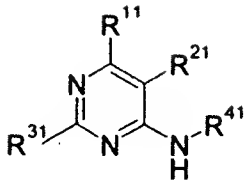
[Table 8]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
12	R^{11} : Me R^{21} : -H R^{31} : 4-Br-3,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.28(3H,s),2.68(2H,t),3.30-3.70(2H,br),6.09(1H,d),6.15(1H,s),6.32(1H,s),7.27(1H,d),7.50-7.65(1H,br),7.78(1H,dd),7.80-7.95(1H,m),11.2-11.7(1H,br) FMS:421.
13 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Cl-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.46(3H,s),2.70-2.90(2H,m),3.67-3.80(2H,m),6.20-6.50(2H,m),6.60-7.05(1H,m),7.35-7.55(1H,m),7.95-8.10(2H,m),9.45-10.00(1H,m). FMS:377.
14 (HCl)	R^{11} : Et R^{21} : -H R^{31} : 4-Cl-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:1.24(3H,t),2.70-2.85(4H,m),3.60-3.80(2H,m),6.20-6.50(2H,m),6.60-6.95(1H,m),7.40-7.55(1H,m),7.95-8.10(2H,m),9.40-10.00(1H,m). FMS:391.
15 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Cl-3,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.50(3H,s),2.70-2.90(2H,m),3.70-3.95(2H,m),6.25-6.55(2H,m),6.55-7.00(1H,m),7.30-7.55(1H,m),8.10-8.40(2H,m),9.10-9.80(1H,m). FMS:377.
16 (HCl)	R^{11} : Et R^{21} : -H R^{31} : 4-Cl-3,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:1.24(3H,t),2.70-3.00(4H,m),3.60-3.95(2H,m),6.35-6.58(2H,m),6.58-6.90(1H,m),7.40-7.60(1H,m),8.15-8.42(2H,m),9.10-9.80(1H,m). FMS:391.
17 (fum)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-(6-Me-4-PyO)	NMR:2.11(3H,s),2.27(3H,s),2.63(2H,t),3.53(2H,br),5.92(1H,s),5.96(1H,s),6.29(1H,br),6.33(1H,s),7.44-7.66(2H,m),7.95(1H,br). FMS:375.

[0062]

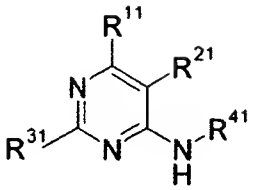
[Table 9]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
18	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-6-Cl-4-PyO)	NMR:2.27(3H,s),2.82(2H,t),3.57(2H,br),6.29(1H,br),6.47(1H,br),6.85(1H,s),7.40-7.65(2H,m),7.94(1H,br),11.30(1H,br). FMS:395.
19	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -(CH_2)-4-PyO	NMR:2.29(3H,s),4.41(2H,br),6.12(1H,d),6.17(1H,s),6.39(1H,br),7.29(1H,d),7.50-7.63(1H,m),7.82-7.97(2H,m),11.40(1H,br). FMS:347.
20 (fum)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_3$-4-PyO	NMR:1.75-1.86(2H,m),2.27(3H,s),2.46(2H,t),3.34(2H,br),6.06(1H,d),6.14(1H,s),6.29(1H,s),6.63(2H,s),7.25(1H,d),7.40-7.63(2H,m),7.82-7.98(1H,m). FMS:375.
21 (fum)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_3$-5-PyO	NMR:1.67-1.80(2H,m),2.26(3H,s),2.38(2H,t),3.25-3.50(2H,m),6.22-6.32(2H,m),6.64(2H,s),7.15(1H,s),7.35(1H,d),7.40-7.50(1H,m),7.55-7.65(1H,m),7.85-8.00(1H,m),12.47(2H,brs). FMS:375.
22 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-6-PyO	NMR:2.44(3H,s),2.84(2H,t),3.75-3.85(2H,m),6.18(1H,d),6.25(1H,d),6.63(1H,s),7.43(1H,dd),7.88-7.96(1H,m),8.00-8.10(1H,m),9.55(1H,s). FMS:361.
23 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-(6-HO-4-PyO)	NMR:2.46(3H,s),2.80-2.90(2H,m),3.55-3.82(2H,m),6.02-6.18(1H,m),6.69(1H,s),7.87-8.15(2H,m),9.45-9.70(1H,m). FMS:377.

[0063]

[Table 10]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
24 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-3-PyO	NMR:2.45(3H,s),2.74(2H,t),3.73-3.82(2H,m),6.10(1H,t),6.54(1H,s),7.20-7.26(1H,m),7.28-7.34(1H,m),7.89(2H,d),8.17(2H,d),9.40-9.50(1H,brs). FMS:385,387.
25 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -CH_2CH(OH)-4-PyO	NMR:2.46(3H,s),3.35-4.75(7H,m),6.33(1H,d),6.45(1H,s),6.71(1H,s),7.39(1H,d),7.83-8.12(2H,m),9.67(1H,br). FAB-MS:377.
26 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -CH_2CH(Me)-4-PyO	NMR:1.20(3H,d),2.45(3H,s),2.90-3.08(1H,m),3.45-3.75(2H,m),4.00-5.20(3H,br),6.30-6.42(2H,m),6.69(1H,s),7.41(1H,d),7.84-8.15(2H,m),9.76(1H,br). FAB-MS:375.
27 (HCl)	R^{11} : Me R^{21} : -F R^{31} : 4-Br-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.39(3H,d),2.95(2H,t),3.60-3.80(2H,m),6.72(1H,d),6.78(1H,s),7.75(1H,d),7.82-7.94(2H,m),8.00-10.00(3H,m). FAB-MS:439,441.
28 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 6-Br-3-Py R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.50(3H,s),2.70-2.90(2H,m),3.50-3.95(2H,m),6.38(1H,d),6.42(1H,s),6.64(1H,s),7.46(1H,d),7.83(1H,d),8.20-8.75(1H,m),9.10-9.35(1H,m),9.35-9.75(1H,m). FAB-MS:386,388.

[0064]

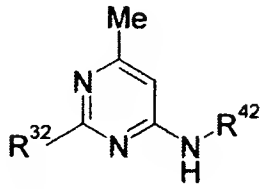
Below, the structures of other compounds of the present invention are shown in Tables 11 to 13. These can easily be prepared using the methods described in the foregoing Preparations and Examples, methods that will be obvious to those skilled in the art, or variations on these methods. Note that, in the tables, the notations have the following meanings.

No.; Compound No.

R^{32}, R^{42}, R^{12} and R^{22}: Substituents in the general formulas (cPr: cyclopropyl, tBu: tertiary butyl).

[0065]

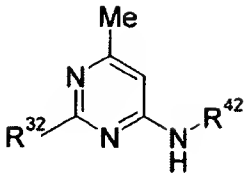
[Table 11]



No	R^{32}	R^{42}
A1	4-Br-2,5-diF-Ph	-CH_2CH(OH)-4-PyO
A2	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-HO_2C-4-PyO)
A3	4-cyano-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A4	4-H_2N-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A5	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-Me-4-PyO)
A6	5-Br-3-Py	-$(CH_2)_2$-4-PyO
A7	4-MeO-Ph	-$(CH_2)_2$-4-PyO
A8	4-O_2N-Ph	-$(CH_2)_2$-4-PyO
A9	4-tBu-Ph	-$(CH_2)_2$-4-PyO
A10	indol-5-yl	-$(CH_2)_2$-4-PyO
A11	5-Br-thiophen-2-yl	-$(CH_2)_2$-4-PyO
A12	4-Br-2,5-diF-Ph	-CH_2CH(Me)-4-PyO
A13	4-Br-2,5-diF-Ph	-$(CH_2)_2$-4-QuiO
A14	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-cyano-4-PyO)
A15	4-HO_2C-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A16	4-H_2NOCHN-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A17	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(3-Me-4-PyO)
A18	4-F_3C-Ph	-$(CH_2)_2$-4-PyO
A19	4-Ph-Ph	-$(CH_2)_2$-4-PyO
A20	benzodioxol-5-yl	-$(CH_2)_2$-4-PyO
A21	4-HO-Ph	-$(CH_2)_2$-4-PyO
A22	benzofuran-5-yl	-$(CH_2)_2$-4-PyO
A23	1-Me-benzimidazol-5-yl	-$(CH_2)_2$-4-PyO
A24	4-Br-2,5-diF-Ph	-CH(Me)CH_2-4-PyO
A25	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-EtO_2C-4-PyO)

[0066]

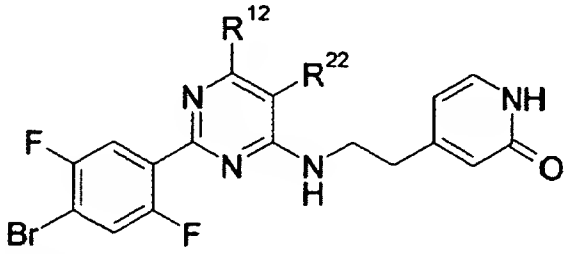
[Table 12]



No	R^{32}	R^{42}
A26	4-EtO_2C-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A27	4-(EtO_2C)HN-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A28	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(5-Me-4-PyO)
A29	6-Cl-3-Py	-$(CH_2)_2$-4-PyO
A30	4-Me_2N-Ph	-$(CH_2)_2$-4-PyO
A31	4-F_3CO-Ph	-$(CH_2)_2$-4-PyO
A32	4-Me-Ph	-$(CH_2)_2$-4-PyO
A33	4-(Me_2N)O_2S-Ph	-$(CH_2)_2$-4-PyO
A34	benzothiophen-5-yl	-$(CH_2)_2$-4-PyO
A35	4-H_2NOC-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A36	4-Br-2,5-diF-Ph	-$(CH_2)_2$-1-PyO

[0067]

[Table 13]



No	R^{12}	R^{22}
A36	Et	Me
A37	Me	Me
A38	cPr	H
A39	Et	F

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	A61K 31/506	A61K 31/506	4C086
	A61P 3/10	A61P 3/10	

(54) **Title of the Invention:** Pyrimidine derivative or salt thereof

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(22) **Application Date:** March 12, 2003

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F Term (Ref.): 4C063 AA01 BB01 CC29 DD12 DD14 EE01
4C086 AA01 AA03 BC42 GA07 GA08 NA14
ZC33

(57) **[Abstract]**

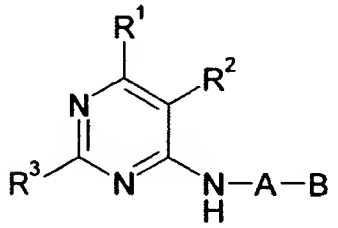
[Problem to Be Solved]

To provide a compound having an excellent effect of promoting insulin secretion and an effect of suppressing blood sugar rise, which can be used in the treatment of insulin-dependent diabetes, non-insulin-dependent diabetes, insulin resistance diseases and obesity.

[Means for Solving the Problems]

The pyrimidine derivative shown in Formula (I) or a pharmaceutically acceptable salt thereof.

[Formula 1]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: -H, -F or methyl.

R^3: an aryl, or aromatic heterocycle, each of which may be substituted.

A: lower alkylene, which may be substituted by one or more –OH.

B: 2-oxopyridyl, which may be substituted and may be condensed with benzene]

[Selected Figure]

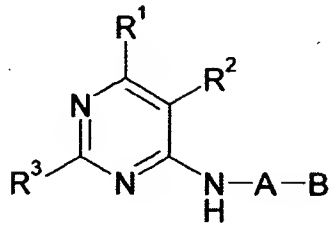
None

[CLAIMS]

[Claim 1]

The pyrimidine derivative shown in Formula (I) or a pharmaceutically acceptable salt thereof.

[Formula 1]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: -H, -F or methyl.

R^3: an aryl, or aromatic heterocycle, each of which may be substituted.

A: lower alkylene, which may be substituted by one or more groups selected from the group consisting of –OH and lower alkyl.

B: 2-oxopyridyl, which may be substituted and may be condensed with benzene]

[Claim 2]

The pyrimidine derivative shown in Formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof, with the exception of the following compounds:

3-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-bromophenyl)-5-fluoro-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,3,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-dichlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3-chloro-4-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one, and

4-(2-{[2-(2,3,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one.

[Claim 3]

A pharmaceutical composition having as an active ingredient a compound shown in Formula (I) according to Claim 1.

[Detailed Description of the Invention]

[0001]

[Technical Field of the Invention]

The present invention relates to a pharmaceutical agent and particularly to a novel pyrimidine derivative, or a pharmaceutically acceptable salt thereof, useful as an agent for promoting insulin secretion or an agent for treating diabetes, and to a medicament having these compounds as an active ingredient thereof.

[0002]

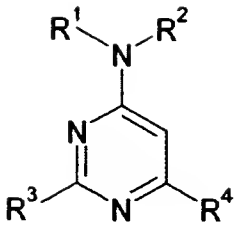
[Prior Art]

Diabetes is a disease primarily characterized by chronic hyperglycemia that develops as a result of relatively or absolutely insufficient insulin action. Clinically, it is broadly divided according to characteristics into insulin-dependent diabetes (hereinafter referred to as "type 1 diabetes") and non-insulin-dependent diabetes (hereinafter referred to as "type 2 diabetes"). One of the major critical causes of type 2 diabetes, which accounts for approximately 90% of diabetics, is decreased insulin secretion from pancreatic β-cells; in particular, postprandial hyperglycemia is observed to result from initial insulin secretion deficiency. Presently, sulphonylurea agents (SU agents) are commonly used as insulin secretion promoters, but these tend to produce hypoglycemia and are known to cause secondary failure due to pancreatic exhaustion in long-term administration. Furthermore, while SU agents are effective for control of blood sugar between meals, suppressing postprandial hyperglycemia is difficult. Recently, large scale clinical trials have confirmed that correction of postprandial hyperglycemia is important in the development of diabetic complications and in controlling progression (Non-Patent Document 1). Furthermore, it has been reported that arterial sclerosis occurs only in the postprandial hyperglycemia period and that persistent mild postprandial hyperglycemia increases death rates due to cardiovascular causes and the like (Non-Patent Document 2). This indicates that, even if mild, postprandial hyperglycemia is an independent risk factor in cardiovascular death. The background described above has resulted in the acknowledgment of the importance and necessity of drug therapies for postprandial hyperglycemia. Accordingly, a pharmaceutical agent having an insulin secretion promoting effect has a profile suitable for correcting postprandial hyperglycemia and/or fasting blood sugar, and may be useful as a therapeutic and prophylactic agent for type 1 diabetes and type 2 diabetes.

[0003]

Meanwhile, pyrimidine derivatives include the compound shown in the following general formula, which is known as an agent used in the treatment of disorders of the circulatory system such as hypertension (Patent Document 1).

[Formula 2]



(See the publication for reference numerals in the formula.)

Note that, in Patent Document 1, diabetes is mentioned as one example of various diseases other than circulatory diseases such as hypertension, but this is not supported by data.

Moreover, in this bulletin, R^4 in the general formula is described in the claims as being a "(C_2-C_5)-alkyl, a trifluoromethyl or an aryl" but specific disclosure in the embodiments is limited to isopropyl, trifluoromethyl, tertiary butyl and phenyl compounds.

[0004]

[Non-Patent Reference 1] *N.Engl. J. Med.*, 329: 977-986, 1993

[Non-Patent Reference 2] *Lancet*, 354:617, 1999, Brit. Med. J., 321: 405-413,2000

[Patent Reference 1] Specification of Unexamined European Patent Application EP-1112266

[0005]

[Problems to Be Solved by the Invention]

As described above, agents for promoting insulin secretion are useful in the treatment and prevention of type 1 diabetes, type 2 diabetes, insulin resistance diseases and obesity; there is therefore a demand for the creation of an agent for promoting insulin secretion having even greater effectiveness.

[0006]

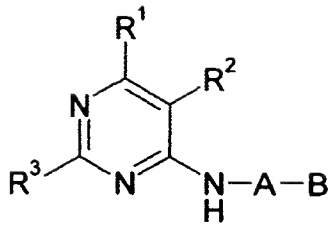
[Means for Solving the Problems]

The present inventors earnestly studied compounds having insulin secretion promotion effects and discovered that a pyrimidine derivative had excellent insulin secretion promotion effects, and thus the present invention was completed.

[0007]

In other words, according to the present invention, the pyrimidine derivative shown in Formula (I), a pharmaceutically acceptable salt thereof, and a pharmaceutical composition having these compounds as an active ingredient, are provided.

[Formula 3]



(I)

[In the formula, the reference symbols have the following meanings.]

R^1: methyl, ethyl or cyclopropyl, which may be substituted by one or more halogen, which may be the same or different.

R^2: H, -F or methyl.

R^3: aryl, or aromatic heterocycle, each of which may be substituted.

A: lower alkylene, which may be substituted by one or more groups selected from the group consisting of –OH and lower alkyl.

B: 2-oxopyridyl, which may be substituted and may be condensed with benzene. Preferably, the pyrimidine derivative shown in Formula (I), or a pharmaceutically acceptable salt thereof, is provided, with the exception of the following compounds.

3-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

5-(2-{[2-(4-bromophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-bromophenyl)-5-fluoro-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,3,5-trifluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,5-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-difluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3,4-dichlorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(3-chloro-4-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(4-chloro-3-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(5-bromo-2-fluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one,

4-(2-{[2-(2,1,3-benzoxadiazol-5-yl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one; and

4-(2-{[2-(2,3,5-trifluorophenyl)-6-ethylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one.

[0008]

Note that, in Formula (I), R^1 is preferably methyl which may be substituted by one or more halogens, which are the same or different, or ethyl substituted by one or more halogens, which are the same or different, (with the exception of trifluoromethyl), and is more preferably methyl.

Furthermore, in Formula (I) R^2 is preferably –H.

Note that, in Formula (I) R^3 is preferably a phenyl or a pyridyl substituted by one or more halogens, which are the same or different, more preferably a phenyl substituted by 2 to 4 halogens, which are the same or different, and particularly preferably a phenyl substituted by 2 to 4 halogens, which are the same or different, including at least one fluorine.

Furthermore, in Formula (I), A is preferably ethylene, which may be substituted by one or more groups selected from the group consisting of –OH and lower alkyl.

Furthermore, in Formula (I), B is preferably 2-oxopyridyl, which may be substituted by one or more groups selected from the group consisting of lower alkyl, halogen and –OH; more preferably 2-oxopyridine-3-yl, 2-oxopyridine-4-yl or 2-oxopyridine-5-yl, which may be substituted by one or more groups selected from the group consisting of lower alkyl, halogen and –OH.

Furthermore, 2-oxopyridine-4-ylethyl is particularly preferred as –A-B in formula (I).

[0009]

The compound of the present invention shown in Formula (I) is characterized in terms of chemical structure by the fact that the amino group in position 4 of the pyrimidine is substituted by

a 2-oxopyridyl alkyl group and is pharmaceutically characterized by having an effect of promoting insulin secretion.

[0010]

[Modes of Embodiment of the Invention]

The compound represented by Formula (I) is as described hereinafter.

In the definition of the general formulas in the present specification, unless otherwise specified, the term "lower" refers to straight or branched carbon chains, comprising one to six carbon atoms.

Accordingly, the term "lower alkyl" refers to a C_{1-6} alkyl, and specific examples are methyl, ethyl, propyl, butyl, pentyl, or structural isomers thereof, such as hexyl, isopropyl, isobutyl or the like; C_{1-4} alkyls are preferred, and methyl and ethyl are more preferred.

"Lower alkylene" means a C_{1-6} alkylene, and specific examples thereof include methylene, ethylene, trimethylene, tetramethylene, pentamethylene, or hexamethylylene or structural isomers thereof, such as methyl methylene or methyl ethylene, preferably a C_{1-4} alkylene, and more preferably methylene, ethylene and trimethylene.

"Aryl" means a monovalent C_{6-14} aromatic hydrocarbon ring group that is monocyclic to tricyclic, preferably phenyl or naphthyl, and more preferably phenyl. "Aromatic heterocycle" means a monovalent aromatic heterocyclic group, which may be condensed with a benzene ring having one to four identical or different heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur, specifically, pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, furazanyl, pyridyl, pyranyl, thiopyranyl, pyridazyl, pyrimidyl, pyrazyl, indolyl, isoindolyl, indolizinyl, benzofuryl, benzothienyl, benzoimidazolyl, indazolyl, benzooxazolyl, benzothiazolyl, benzooxadiazolyl, quinolyl, isoquinolyl, chromenyl, benzothiopyranyl, phthalazinyl, naphthylizinyl, quinoxalinyl, quinoxazolinyl, cinnolinyl, benzodioxolyl, benzodioxinyl, benzodioxepinyl, carbazolyl, or the like; the nitrogen and the sulphur atoms that constitute these rings may be oxidized; in addition, these rings may be partially saturated. Pyridyl, furyl, thienyl, imidazolyl, thiazolyl, oxidopyridyl, pyrazyl, indolyl, benzofuryl, benzothienyl, benzoimidazolyl, benzooxazolyl, benzothiazolyl, benzooxadiazolyl, quinolyl, oxidoquinolyl, isoquinolyl, chromenyl, benzodioxolyl, benzodioxinyl, and benzodioxepinyl are preferred.

"Halogen" includes fluoro-, chloro-, bromo- and iodo-. Fluoro-, chloro- and bromo- are preferred.

[0011]

In the present specification, substituents acceptable [as relates to] the term "which may be substituted" or "substituted" can be any substituent normally used as a substituent for these groups, and may include more than one substituent for each of these groups. Substituents acceptable in terms of "aryl or aromatic heterocycles, which may each be substituted" for R^3, and "2-oxopyridyl, which may be substituted and may be condensed with benzene" for B include the groups cited in (1) to (8) below. Note that "R^{A}" indicates a lower alkyl, which may be substituted by one or more groups selected from the group consisting of -OH, -O-lower alkyl, amino which may be substituted by

one or two lower alkyls, carbonyl which may be substituted by one or two lower alkyls, aryl, an aromatic heterocycle and halogen.

(1) halogen;

(2) -OH, -O-R^A, -O-aryl, -OCO-R^A, oxo(=O);

(3) -SH, -S-R^A, -S-aryl, -SO-R^A, -SO-aryl, -SO_2-R^A, -SO_2-aryl, sulfamoyl, which may be substituted by one or two of R^A;

(4) an amino, which may be substituted by one or two of R^A, -NHCO-R^A, -NHCO-aryl, -$NHCO_2$-R^A, -$NHCONH_2$, -NHCONH-R^A, -$NHSO_2$-R^A, -$NHSO_2$-aryl, nitro;

(5) -CHO, -CO-R^A, -CO_2H, -CO_2-R^A, cyano or carbamoyl, which may be substituted by one or two of R^A;

(6) aryl or cycloalkyl, each of which may be substituted by one or more groups selected from the group consisting of: -OH, -O-lower alkyl, amino, which may be substituted by one or two of R^A, halogen and R^A;

(7) aromatic heterocycle or a non-aromatic heterocycle, which may be substituted by one or more groups selected from the group consisting of: -OH, -O-lower alkyl, amino, which may be substituted by one or two of R^A, halogen and R^A;

(8) lower alkyl, which may be substituted by one or more groups selected from the groups set forth in (1) to (7) above.

Herein, "cycloalkyl" refers to monovalent C_{3-10} carbocyclic groups, and these rings may be crosslinked. Specific examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl, norbornyl, and adamanthyl.

The term "non-aromatic heterocycle" means a monovalent non-aromatic heterocyclic group having 1 to 4 heteroatoms chosen from amongst the group consisting of nitrogen, oxygen and sulfur which may be the same or different, and specific examples include: oxetanyl, pyrrolidinyl, tetrahydrofuryl, tetrahydrothiofuryl tetrahydrothiopyranyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperadinyl, morpholinyl, thiomorpholinyl, and quinuclidinyl; the nitrogen and the sulphur atoms that constitute these rings may be oxidized. Pyrrolidinyl, piperidinyl, piperadinyl, and morpholinyl are preferred.

Furthermore, the substituents for "2-oxopyridyl, which may be substituted and may be condensed with benzene" in B, may be substituted at the nitrogen in the pyridyl, which is to say, at position 1 in the 2-oxopyridyl.

[0012]

The compound represented by Formula (I), depending on the type of substituents, may contain an asymmetric carbon atom, and an optically active substance may exist as a result. The present invention includes all the mixtures and isolates of these optical isomers. Furthermore, tautomers may exist for the compound shown in Formula (I), and the present invention includes both separated isomers and mixtures thereof.

In addition, there may be cases where the compounds shown by Formula (I) form salts, which are included in the present invention, as long as such salts are salts that are pharmaceutically acceptable. Specifically, acid addition salts of inorganic acids, such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid and phosphoric acid; organic acids, such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, aspartic acid and glutamic acid; salts of inorganic bases containing metals, such as sodium, potassium, magnesium, calcium and aluminum; salts of organic bases, such as methylamine, ethylamine, ethanolamine, lysine and ornithine; and ammonium salts and the like may be cited.

Furthermore, the present invention also includes substances comprising various hydrates, solvates, or crystal polymorphs of the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention or pharmaceutically acceptable salts thereof. In addition, the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention also includes all compounds that are metabolized *in vivo* and converted into the compounds shown by Formula (I) or the salt thereof, so-called prodrugs. As groups that form prodrugs of the compound that is the active ingredient of the pharmaceutical agent of the present invention or the compound of the present invention, the groups described in *Prog. Med.* 5:2157-2161 (1985) and groups described in "Development of Pharmaceuticals, " volume 7, *Molecular Design,* pp. 163-198, Hirokawa Shoten (1990) may be cited.

[0013]

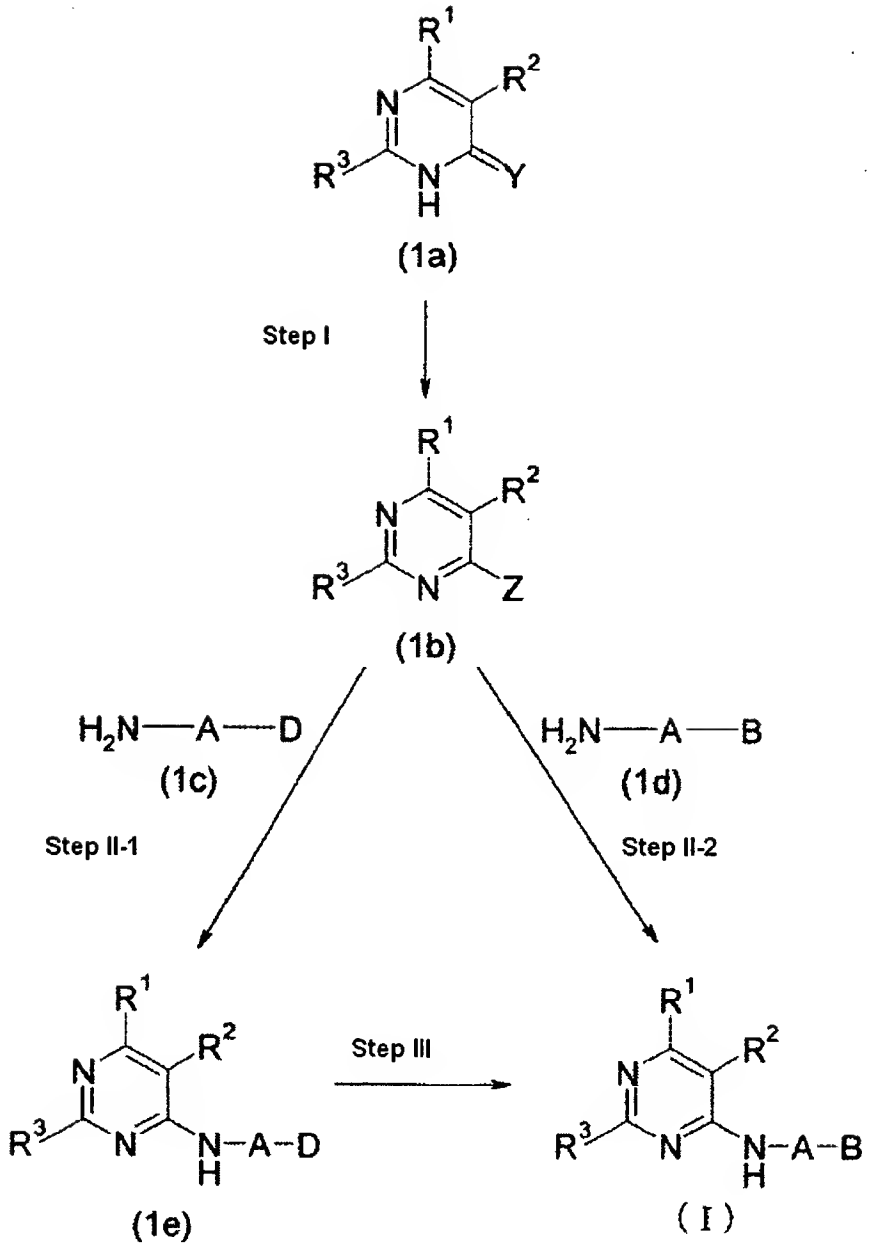
[Manufacturing Method]

The compound shown by Formula (I) or the salt thereof may be manufactured by applying a variety of well-known synthesis methods using characteristics that are based on the basic backbone or the type of substituents. Representative preparations are illustrated below. In addition, depending on the type of functional group, there may be cases where it is effective, in terms of manufacturing technology, to replace, at the raw material or intermediate stage, the functional group in question with a suitably protected group, i.e., a group that can be easily reverted into the functional group in question. Thereafter, the protective group can be eliminated as necessary to obtain the desired compound. For example, such functional groups include the hydroxyl group or the carboxyl group or the amino group, and protective groups therefor include the protective groups described, for instance, in *Protective Groups in Organic Synthesis,* 3rd ed., by Greene and Wuts; these may be used as is suitable according to reaction conditions.

[0014]

Preparation 1

[Formula 4]



(In the scheme, A, B, R^1, R^2 and R^3 have the same meaning as described above; Y indicates O or S; Z indicates a leaving group; and D indicates 2-(lower alkyl-oxy)pyridyl, which may be substituted or condensed with benzene (same hereinafter).)

This preparation is a method in which a pyrimidine derivative, which has a leaving group, shown by Formula (1b), and which can be prepared by halogenation or sulfonylation of the pyrimidinone or pyrimidinethione derivative shown by Formula (1a) according to ordinary methods, is acted upon by an amine having the 2-alkoxypyridyl group or the 2-pyridyl group shown in

Formula (1c) or (1d), and subjected to a dealkylation reaction as necessary, to manufacture the compound of the present invention represented by Formula (I).

The leaving group indicated by Z in Compound (1b) represents a group that can be eliminated in the form of HZ with a hydrogen atom from the amino group of Compound (1c) or (1d) under reaction conditions, and includes, for example, halogens, such as fluoro-, chloro-, bromo-, and iodo-, lower alkylsulfonyloxy groups, such as methanesulfonyloxy, perhalogenomethanesulfonyloxy groups, such as trifluoromethanesulfonyloxy, and arylsulfonyloxy groups, such as benzenesulfonyloxy and p-toluenesulfonyloxy.

Step I

Halogenation in this step is carried out by reacting, for instance, Compound (1a) with a halogenation agent, such as phosphorus oxychloride or phosphorus tribromide. Sulfonylation is carried out by reacting, for instance, Compound (1a) where Y is an oxygen atom and a sulfonylation agent, such as methanesulfonylchloride, p-toluenesulfonylchloride, trifluoromethanesulfonylchloride, or trifluoromethanesulfonic acid anhydride.

Compound (1a) can be prepared by well-known methods, for instance, the methods described in *J. Am. Chem. Soc.*, 74, 842 (1952), *Chem. Ber.*, 95, 937 (1962), or *J. Org. Chem.*, 29, 2887 (1964), or methods based on these methods. Furthermore, compound (1a) is commercially available and can be prepared by well-known methods other than those mentioned above.

Step II-1

In this step, reaction between Compound (1b) and Compound (1c) is carried out at normal pressure or under pressure, without a solvent or in a suitable solvent.

Specific examples of solvents include aromatic hydrocarbons, such as toluene and xylene; ketones, such as methylethylketone and methylisobutylketone; ethers, such as ether, tetrahydrofuran (THF), dioxane, and diglyme; alcohols, such as methanol (MeOH), ethanol (EtOH), and 2-propanol; acetonitrile, dimethylformamide (DMF), 1,3-dimethyl-2-imidazolidinone (DMI), dimethylsulfoxide (DMSO), water, or a solvent that is a mixture of these. It is preferred that this reaction be carried out in the presence of a base. Specific examples of bases include alkaline carbonates, such as sodium carbonate and potassium carbonate; alkaline hydrogen carbonates, such as sodium bicarbonate and potassium hydrogen carbonate; tertiary amines, such as triethylamine and diisopropylethylamine, and the like, and may also be combined with an excess amount of Compound (1c). The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 20°C and approximately 180°C, preferably between approximately 60°C and approximately 130°C.

Step II-2

This step is performed based on Step II-1 of Preparation 1.

Step III

The reaction for dealkylation of the Compound (1e) in this step is carried out at normal pressure or under pressure, without a solvent or in a suitable solvent. Examples of dealkylation

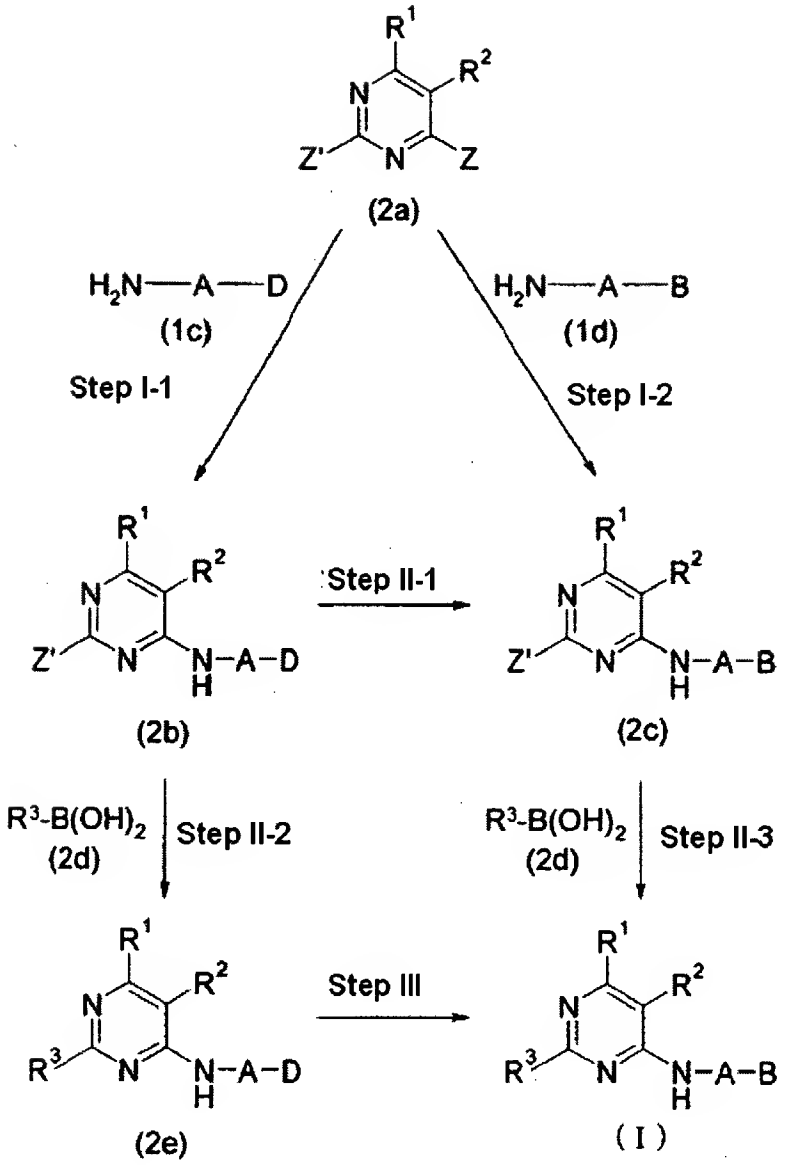
agents used in this reaction include inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid and phosphoric acid; organic acids such as formic acid, acetic acid and trifluoroacetic acid; Lewis acids such as borontrifluoride etherate complex and aluminum chloride; and iodotrimethylsilane.

Specific examples of solvents include chloroform, ethanethiol, water and mixtures of these solvents, and these can also be combined with an excess amount of acid. The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 0°C and approximately 120°C, preferably between approximately 20°C and approximately 100°C.

[0015]

Preparation 2

[Formula 5]



(In the scheme, Z' indicates the leaving group.)

This preparation is a method in which a pyrimidine derivative having two leaving groups represented by Formula (2a) undergoes the action of an amine having a 2-alkoxypyridine group or a 2-pyridonyl group represented by Formula (1c) or (1d), and is subjected to a dealkylation reaction as necessary, to allow the preparation of a pyrimidine derivative having a leaving group represented by Formula (2b) or (2c), which undergoes the action of the boron derivative represented by Formula (2d), and is subjected to a dealkylation reaction as necessary, to manufacture the compound of the present invention shown by the Formula (I).

The leaving group indicated by Z' in Compounds (2a), (2b) and (2c) is the same as the leaving group indicated by Z in Compound (1b) shown in Preparation 1, and Z and Z' may be the same or different.

Step I-1 and Step I-2

These steps are performed based on Step II-1 and Step II-2 of Preparation 1.

Step II-1 and Step III

These steps are performed based on Step III in Preparation 1.

Step II-2 and Step II-3

The condensation reactions in these steps are carried out at normal pressure or under pressure, without a solvent or in a suitable solvent.

Specific examples of solvents include aromatic hydrocarbons, ketones, ethers, alcohols, acetonitrile, DMF, DMSO, water, or a solvent that is a mixture thereof. It is preferred that the present reaction be carried out in the presence of a base, and specific examples of bases include alkaline carbonates, alkaline hydrogen carbonates, tertiary amines, and the like. The reaction temperature differs according to the type of the raw material compound, the reaction conditions, and the like, and is generally between approximately 20°C and approximately 180°C, preferably between approximately 60°C and approximately 130°C.

Furthermore, this reaction may advance smoothly as a result of adding transition metals or transition metal-phosphine complexes. Specific examples thereof include palladium-carrying carbon, dichloro[1,4-bis(diphenylphosphine)butane]palladium, tetrakis(triphenylphosphine)palladium, and the like; those described in specific examples in U.S. Patent Publication No. 5550236 can also be used.

[0016]

Furthermore, some compounds shown by Formula (I) can also be prepared from compounds obtained in the manner described above, by combining any processes conventionally used by those skilled in the art, such as well-known alkylation, acylation, oxidation, and reduction.

[0017]

The compound of the present invention manufactured in this way is isolated/purified, either in free form or as a salt thereof, using ordinary salt formation processes. Isolation/purification is carried out by applying ordinary chemical operations, such as extraction, concentration, evaporation, crystallization, filtration, recrystallization, precipitation, and various chromatographies.

Various isomers can be isolated by ordinary methods, using the differences in physicochemical properties between the isomers. For instance, racemic mixtures can be used to produce an optically pure isomer by common separation methods for racemic bodies, such as, for instance, a method in which a diastereomeric salt is produced with a generic optically active acid, such as tartaric acid, and resolved optically. In addition, diastereo mixtures can be separated, for instance, by fractional crystallization or various chromatographies. In addition, optically active compounds can be manufactured by using raw materials with suitable optical activity.

[0018]

[Effects of the Invention]

The compound of the present invention as indicated by Formula (I) has an excellent effect of promoting insulin secretion and an effect of suppressing blood sugar rise. Consequently, based on these effects, the compound shown by Formula (I) is useful in the treatment and/or prophylaxis of type 1 diabetes, type 2 diabetes, insulin resistance diseases, and/or obesity.

[0019]

The pharmacological effects of the compound of the present invention have been verified by the following test methods.

(1) Test for measuring the effect of promoting insulin secretion

In this test, the effect of promoting insulin secretion was examined for the test compound using MIN6 cells or MIN6B1 cells, which are mouse pancreatic β cell strains. The test method is described below.

MIN6 cells or MIN6B1 cells were sown in a 24-well plate so as to obtain 2 x 10^5 cells/well (0.4 ml) (culture medium used was DMEM containing 25 mM glucose to which FCS was added to 10%). After 2 days, the culture medium was removed with an aspirator, washed once with 1 ml of KRB-HEPES (140 mM NaCl, 3.6 mM KCl, 0.5 mM NaH2PO4, 0.5 mM $MgSO_4$, 1.5 mM $CaCl_2$, 2 mM $NaHCO_3$, 0.1% BSA, and 10 mM HEPES (pH 7.4)) containing 2.8 mM glucose warmed to 37°C; 1 ml of the same buffer solution was introduced again and incubated for between 30 minutes and 60 minutes at 37°C. The buffer solution was removed with an aspirator; 0.5 ml of each of KRB-HEPES containing 16.8 mM glucose to which 10 μM each of test compound had been added was added to each well and incubated for 22 minutes at 37°C. The samples were fractionated, and 2.0 μl to 2.5 μl were diluted in 50 μl of PBS; insulin concentration was determined using the Phadeseph insulin RIA kit (manufactured by Pharmacia, Upjohn) or a rat insulin [^{125}I] assay system RPA549 (Amersham Biosciences). The test compound was dissolved in 100% DMSO and added at a final concentration of 0.1%. The activity was expressed as a relative ratio where DMSO is 100%. The results are shown in Table 1.

Note that, in the description of the compounds in the table, "Ex" indicates the example number of the example compound described below (same hereinafter).

[0020]

[Table 1]

Compound	Insulin secretion promoting effect (%)
Ex 5	206
Ex 9	153
Ex 18	148
Glibenclamide	122

As described above, the compound of the present invention showed a strong effect of promoting insulin secretion.

[0021]

[*sic Paragraph 0021 in the original Japanese publication contains no text. – trans.*]

[0022]

(2) Test by oral sugar loading with normal mouse

In this test, the activity of the test compound in terms of suppressing blood sugar rise after sugar loading was examined using a normal mouse. The test method is described below.

An ICR mouse (male, 6 weeks old), prebred for 1 week, was fasted for 18 to 20 hours and used as test animal. The test compound was dissolved in water and administered orally at 3 mg/kg (10 mg/kg for Nateglinide) 5 minutes prior to glucose load (30 minutes before for Nateglinide). The rate of blood sugar decrease (%) versus the control group 30 minutes after glucose loading was measured. The results are shown in Table 2.

[0023]

[Table 2]

Compound	Rate of blood sugar decrease (%)
Ex 14	25
Nateglinide	26

As described above, the compound of the present invention showed a strong blood sugar lowering effect in the oral sugar loading test with the normal mouse.

[0024]

The pharmaceutical agent of the present invention can be prepared by methods used conventionally, using one or more of the compounds indicated by Formula (I) and an agent carrier, an excipient, and other additive agents used in conventional formulation. Administration may be in any form, including oral administration of tablets, pills, capsules, granules, powders, subtle granules, solutions, and the like; parenteral administration, such as via injectables, such as intravenous injection and intramuscular injection; or suppository, nasotracheal, transmucosal, percutaneous, and the like.

Tablets, powders, granules, and the like can be used as solid compositions for oral administration of the present invention. In such solid compositions, one or more active substance is mixed with at least one inert diluent, such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium aluminate metasilicate, or the like. According to methods of the art, the composition may contain an additive agent in addition to the inert diluent, for instance, a lubricant, such as magnesium stearate; a disintegrant, such as fibrous calcium gluconate; a stabilization agent, such as lactose; a solubilizer, such as glutamic acid or aspartic acid; or a dissolution adjuvant. Tablets or pills may be coated as necessary with a

sugar coating, such as sucrose, gelatin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose phthalate, or a film soluble in the stomach or intestine.

[0025]

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, and the like, and includes commonly used inert diluents, such as purified water and EtOH. Such compositions may contain, in addition to the inert diluent, adjuvants, such as a solubilizer, a dissolution adjuvant, a wetting agent, a suspensioning agent, as well as sweetening agents, flavoring agents, aroma agents, and preservatives.

Injectables for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, and emulsions. Diluents for aqueous solutions and suspensions include, for instance, distilled water and physiological saline for injectables. As diluents for non-aqueous soluble solutions and suspensions, for instance, propyleneglycol, polyethyleneglycol, plant oils, such as olive oil, alcohols, such as EtOH, and Polysorbate 80 (product name) are available. Such compositions may further contain additive agents, such as an isotonization agent, preservatives, a wetting agent, an emulsifying agent, a dispersant, a stabilization agent, such as, for instance, lactose, a solubilizer, or a dissolution adjuvant. These are sterilized by, for instance, filtration in which this is passed through a bacteria-retaining filter, mixing this with bactericide, or bombardment. These may also be used by producing them as sterile solid compositions and dissolving these in sterile water or a sterile injectable solvent prior to use.

In case of conventional oral administration, a daily dose of 0.1 to 500 mg per adult is adequate, and this is administered once or separated into two to four doses. In case of intravenous administration, a daily dose of 0.01 to 100 mg per adult is adequate, and this is administered once or separated into two to four doses. The dose is determined optimally according to each case considering the symptoms, age, body weight, sex, and the like. Since the dose varies due to a variety of factors, an amount less than the administration range described above may be sufficient.

[0026]

[Examples]

The present invention will be described below by way of examples; however, the present invention is not limited in any way by these examples. In addition, the raw material compounds used in the examples also contain novel substances, and description will be given using the preparation of such raw material compounds from well-known compounds as reference examples.

[0027]

Reference Example 1

After stirring a mixture of 31.32 g of 4-bromo-2,5-diflurobenzoic acid, 100 ml of thionyl chloride and 0.5 ml of DMF for 2 hours at 80°C, 200 ml of toluene was added and the solvent was evaporated *in vacuo*. 200 ml of chloroform was added to the residue and 200 ml of 28% ammonia water was instilled in ice and this was stirred for 1 hour at the same temperature. The reaction solution was extracted with chloroform, and after washing the organic layer with a saturated saline

solution (brine), this was dried with anhydrous magnesium sulfate (M_GSO_4). The solvent was evaporated *in vacuo* to produce 28.42 g of 4-bromo-2,5-difluorobenzamide as a light yellow solid.

The compound of Reference Example 2 was produced in the same manner as Reference Example 1.

[0028]

Reference Example 3

A mixture of 28.37 g of 4-bromo-2,5-difluorobenzamide and 115 ml of phosphorus oxychloride was stirred for 1.5 hours at 80°C, whereafter 250 ml of toluene was added and the solvent was evaporated *in vacuo*. 300 ml of ice water was added to the residue, and after extraction with ether, the organic layer was washed with saturated aqueous sodium bicarbonate and brine, followed by drying with M_GSO_4. The solvent was evaporated *in vacuo* to produce 26.82 g of 4-bromo-2,5-difluorobenzonitrile as a yellow solid.

The compound of Reference Example 4 was produced in the same manner as Reference Example 3.

[0029]

Reference Example 5

Hydrochloric acid gas was blown for 30 minutes at –65°C into a mixture of 18.20 g of 4-bromobenzonitrile, 300 ml of chloroform, and 100 ml of EtOH while stirring, which was subsequently stirred overnight at room temperature. After evaporating the solvent *in vacuo*, 48 g of ammonium carbonate and 400 ml of EtOH were added to the residue and stirred for 3 days at room temperature. After adding 300 ml of water to the reaction solution, EtOH was evaporated *in vacuo*, and the deposited solids were collected by filtration, rinsed, and 22.91 g of 4-bromobenzamidine hydrochloride was obtained as colorless solids.

The compounds of Reference Examples 6 to 9 were obtained in the same way as in Reference Example 5.

[0030]

Reference Example 10

9.72 g of sodium methoxide was added to 250 ml MeOH solution of 14.13 g of 4-bromobenzamidine hydrochloride, and after stirring for 30 minutes at room temperature, 7.50 ml of methyl acetoacetate was added, and this was stirred for 20 hours at 60°C. To the reaction solution, 400 ml of aqueous solution of 1 M HCl was added under ice-cold conditions, the deposited solids were collected by filtration, rinsed, and 13.98 g of 2-(4-bromophenyl)-6-methyl-3H-pyrimidine-4-one was obtained as colorless solids.

The compounds of Reference Examples 11 to 15 were obtained in the same way as in Reference Example 10.

[0031]

Reference Example 16

A mixture of 8.80 g of 2-(4-bromophenyl)-6-methyl-3H-pyrimidine-4-one and 80 ml of phosphorus oxychloride was stirred for 2 hours at 80°C. After the solvent was evaporated *in vacuo*, 100 ml of ice water and 150 ml of an aqueous solution of 1 M NaOH were added successively to the residue, the deposited solids were collected by filtration, rinsed, and 10.13 g of 2-(4-bromophenyl)-4-chloro-6-methylpyrimidine was obtained as colorless solids.

The compounds of Reference Examples 17 to 21 were obtained in the same way as in Reference Example 16.

[0032]

The structures and the physical data for the Reference Example compounds are shown in Tables 3 to 5. Note that the notations in the table have the following meanings (same hereinafter):

Rf: Reference Example number

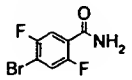
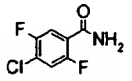
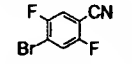
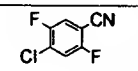
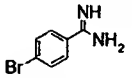
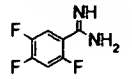
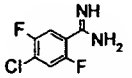
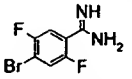
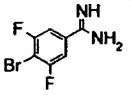
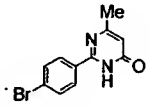
Data: Physical data, FMS: mass spectrometric data (if not otherwise specified, FAB-MS$(M+H)^+$ data), NMR: NMR data ($(CH_3)_4Si$ serves as the internal reference, and if not otherwise specified, δ (ppm) of the peak in ^{1}H-NMR with DMSO-d_6 as the measurement solvent)

Salt: salt (HCl: hydrochloride, HBr: hydrobromic acid salt, fum: fumarate, Ox: oxalate, unless otherwise specified: free-body)

Structure: chemical structure formula, Me: methyl, Et: ethyl.

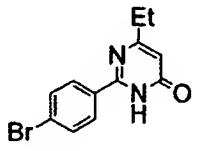
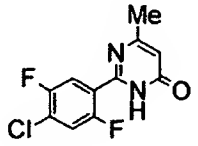
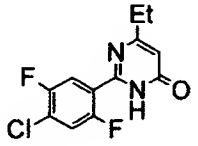
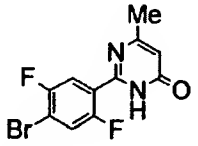
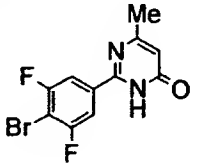
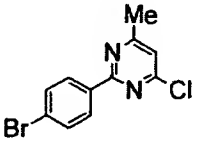
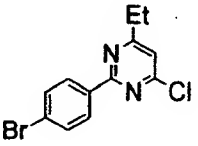
[0033]

[Table 3]

Rf (Salt)	Structure	Data
1		FMS:236,238.
2		FMS:192.
3		EI-MS(M^+):217,219.
4		EI-MS(M^+):173.
5 (HCl)		FMS:199,201.
6		FMS:175.
7		FMS:191.
8		EI-MS(M^+):234,236.
9		FMS:237.
10		FMS:265,267.

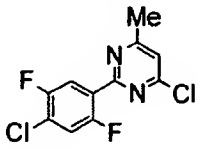
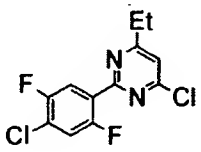
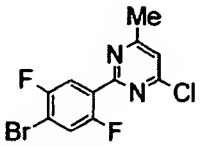
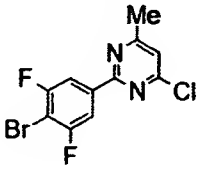
[0034]

[Table 4]

Rf (Salt)	Structure	Data
11		FMS:279,281.
12		FMS:257.
13		FMS:271.
14		FMS:301,303.
15		FMS:301,303.
16		FMS:285.
17		FMS:299.

[0035]

[Table 5]

Rf (Salt)	Structure	Data
18		FMS:275.
19		FMS:289.
20		FMS:321.
21		FMS:319,321.

[0036]

Reference Example 22

An amount of a 200 ml THF solution of 19.06 g of methyl 2-methoxyisonicotinate was added to a mixture of 4.33 g of lithium aluminium hydride and 340 ml of THF under ice-cold conditions and stirred for 1 hour at the same temperature.

Under ice-cold conditions, 70 ml of aqueous THF (1:1) were added to the reaction liquid and, after filtering over Celite, the solvent was evaporated *in vacuo* to produce 16.96 g of (2-methoxypyridine-4-yl)methanol as an oily, orange-colored substance.

FAB-MS$(M+H)^+$:140.

[0037]

Reference Example 23

After instilling 89 ml of thionyl chloride into 16.96 g of (2-methoxypyridine- 4-yl)methanol under ice-cold conditions, this was stirred for 2.5 hours at the same temperature, and then stirred for a further 4 hours at room temperature. After evaporating the solvent *in vacuo*, the saturated aqueous solution of sodium bicarbonate was added to the residue and this was extracted with chloroform.

The organic layer was dried with $MgSO_4$, whereafter the solvent was evaporated *in vacuo* to produce 15.06 g of 4-(chloromethyl)-2-methoxypyridine as an oily brown substance.

FAB-MS$(M+H)^+$:158.

[0038]

Reference Example 24

A mixture of 15.06g of 4-(chloromethyl)-2-methoxypyridine, 12.44 g of potassium cyanide, 25.26 g of 18-crown-6-ether and 300 ml of acetonitrile was stirred for 12 hours at room temperature. After evaporating the solvent *in vacuo*, 400 ml of water was added to the residue and this was extracted with ethyl acetate (EtOAc). After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 9.51 g of (2-methoxypyridine-4-yl) acetonitrile as a yellow solid.

FAB-MS$(M+H)^+$:149.

[0039]

Reference Example 25

Raney nickel (suspension) was added to a solution of 9.51 g of (2- methoxypyridine-4-yl) acetonitrile in 100 ml of EtOH and 25 ml of ammonia water, under hydrogen atmosphere, and stirred for 8 hours at room temperature. After the reaction solution was filtered over Celite, the solvent was evaporated *in vacuo*, and 9.06 g of 3-(2-aminoethyl)-2-methyl pyridine was obtained as an oily, brown substance.

FAB-MS$(M+H)^+$:153.

[0040]

Reference Example 26

A mixture of 15.0 g (6-methoxypyridine-3-yl)methanol, 228 g of magnesium dioxide and 400 ml of acetone was stirred for two days at room temperature. After filtering the reaction solution and evaporating the solvent *in vacuo*, the deposited solids were collected by filtration and washed with hexane to produce 7.05 g of 6-methoxynicotine aldehyde as colorless solids.

FAB-MS$(M+H)^+$:138.

[0041]

Reference Example 27

2.83 g of a 60% oil suspension of sodium hydride was added to a 100 ml THF solution of 11.6 of triethyl phosphonoacetate under ice-cold conditions, and this was stirred for 10 minutes at the same temperature, whereafter a 50 ml THF solution of 5.92 g of 6-methoxynicotine aldehyde was added and this was stirred at room temperature for 2 hours.

Ice water was added to the solution and this was extracted with EtOAc, whereafter the organic layer was washed with saturated saline and dried with $MgSO_4$.

After evaporating the solvent *in vacuo*, the residue was purified by silica gel column chromatography (hexane : EtOAc) to produce 7.52 g of ethyl (2E)-3-(6-methoxypyridine-3-yl) acrylate as a colorless oily substance.

FAB-MS(M+H)$^+$:208.

[0042]

Reference Example 28

750 mg of 10% palladium-carrying carbon was added to a 100 ml EtOH solution of 7.50 g of ethyl (2E)-3-(6-methoxypyridine-3-yl) acrylate, and this was stirred for 2 hours at room temperature in a hydrogen atmosphere. After the reaction solution was filtered over Celite, the solvent was evaporated *in vacuo*, and 7.57 g of ethyl 3-(6-methoxypyridine-3-yl)propionate was obtained as colorless oily substance.

FAB-MS(M+H)$^+$:210.

[0043]

Reference Example 29

38.1 ml of n-butyllithium (1.5 M hexane solution) was instilled into a 100 ml THF solution of 5.86 g of 2-methoxy-6-methylpyrimidine, whereafter 7.94 g of paraformaldehyde was added, and this was stirred overnight at room temperature. Ice water was added to the reaction solution and this was extracted with EtOAc, whereafter the organic layer was washed with brine and dried with $MgSO_4$. After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 1.68 g of 2-(6-methoxypyridine- 2-yl)ethanol as a colorless oily substance.

NMR:2.79(2H,t),3.72-3.76(2H,m),3.82(3H,s),4.59(1H,t),6.61(1H,d),6.83(1H,d),7.56-7.62(1H,m).

[0044]

Reference Example 30

A mixture of 2.05 g of 5-(chloromethyl)-2-methoxypyridine, 2.65 g of phthalimide potassium and 20 ml of DMF was stirred for two hours at 100°C. Ice water was added to the reaction solution, and the deposited solids were collected by filtration and washed to produce 1.91 g of 2-[(6-methoxypyridine-3-yl)methyl]-1H-isoindol- 1,3(2H)-dione as colorless solids.

FAB-MS(M+H)$^+$:269.

[0045]

Reference Example 31

A mixture of 1.91 g of 2-[(6-methoxypyridine-3-yl)methyl]-1H-isoindol-1,3(2H)-dione, 1.7 ml of hydrazine hydrate and 20 ml of MeOH was stirred overnight at room temperature, whereafter the reaction solution was filtered and the solvent was evaporated. 30 ml of 1M aqueous NaOH was added to the residue and this was extracted with chloroform. The organic layer was washed with brine and dried with $MgSO_4$, whereafter the solvent was evaporated *in vacuo* to produce 700 mg of [(6-methoxypyridine-3-yl)methyl]amine.

FAB-MS(M+H)$^+$:139.

[0046]

Reference Example 32

To a 200 ml DMF solution of 10.7 g of 2-methoxyisonicotinic acid were successively added under ice-cold conditions 10.4 g of 1-hydroxybenzotriazole, 14.8 g of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 7.51 g of N,O-dimethylhydroxylamine hydrochloride and 21.4 ml of trimethylamine, and this was stirred at room temperature for 20 hours. After evaporating the solvent *in vacuo*, water was added and this was extracted with EtOAc. After washing the organic layer with saturated aqueous sodium bicarbonate and drying with $MgSO_4$, the solvent was evaporated *in vacuo*. The residue was purified by silicone gel chromatography (chloroform : MeOH : ammonia water) to produce 13.4 g of N,2-dimethoxy-N-methylisonicotinamide.

FAB-MS$(M+H)^+$:197.

[0047]

Reference Example 33

22.3 ml of a 1.2 M methyllithium ether solution was instilled into a 100 ml THF solution of 5.0 g of N,2-dimethoxy-N-methylisonicotinamide at 78°C, whereafter this was warmed to room temperature while stirring. Water was added to the reaction solution, and after evaporating the solvent *in vacuo*, brine was added to the residue and this was extracted with EtOAc. After drying the organic layer with $MgSO_4$ and evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (hexane : EtOAc) to produce 3.17 g of 1-(2-methoxypyridine-4-yl)ethanone.

EI-MS(M^-):150.

[0048]

Reference Example 34

To a 50 ml DME solution of 1.60 g of 1-(2-methoxypyridine-4-yl)ethanone were successively added at −15°C, 2.17 g of tosylmethyl isocyanide, 2.5 g of butoxypotassium and 5 ml of EtOH, and this was stirred for 3 hours while gradually warming it to room temperature. After evaporating the solvent *in vacuo*, water was added to the residue and this was extracted with ether. After drying the organic layer with $MgSO_4$ and evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (hexane : EtOAc) to produce 3.17 g of 1-(2-methoxypyridine-4-yl)ethanone.

EI-MS(M^-):161.

[0049]

Reference Example 35

A mixture of 1.35 g of 2-methoxyisonicotinenicotine aldehyde, 7.51 g of N,O-dimethylhydroxylamine hydrochloride, 1.63 g of potassium carbonate and 10 ml of EtOH was stirred for 30 minutes at room temperature. After filtering the reaction solution over Celite and evaporating the solvent *in vacuo*, 500 mg of 10% palladium-carrier carbon was added to the residue and this was stirred for 22 hours under a hydrogen atmosphere. After filtering the reaction solution over Celite and evaporating the solvent *in vacuo*, a saturated aqueous solution of sodium bicarbonate was added to the residue and this was extracted with chloroform. After drying the organic layer with $MgSO_4$ and evaporating the solvent *in vacuo*, the residue was purified by silica

gel chromatography (hexane : MeOH : aqueous ammonia) to produce 415 mg of [(2-methoxypyridine-4-yl)methyl]amine.

FAB-MS(M+H)$^+$:139.

[0050]

Reference Example 36

2.05 ml of diethyl cyanomethylphosphonate was added to a 30 ml THF solution of 0.48 of a 60% sodium hydride oil suspension, under ice-cold conditions, and stirred for 30 minutes at the same temperature, whereafter a 20 ml THF solution of 1.50 g of 2-methoxyisonicotine aldehyde was added, and this was stirred for 15 hours at room temperature. Water was added to the residue produced by evaporating the solvent *in vacuo* and this was extracted with EtOH, whereafter the organic layer was washed with brine and dried with $MgSO_4$. After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 1.14 g of 3-(2-methoxypyridine-4-yl) acrylonitrile as colorless solids.

FAB-MS(M+H)$^+$:161.

[0051]

Reference Example 37

2.56 g of sodium cyanide and 8.51 g of diethyl cyanophosphonate were added to an 80 ml THF solution of 2.38 g of 2-methoxyisonicotine aldehyde, and this was stirred for 30 minutes at the same temperature. Water was added to the residue produced by evaporating the solvent *in vacuo* and this was extracted with EtOH, whereafter the organic layer was washed with water and saturated saline and dried with $MgSO_{44}$. After evaporating the organic layer *in vacuo*, the residue was purified by silica gel column chromatography (hexane: EtOAc) to produce 2.22 g of diethyl cyano(2- methoxypyridine-4-yl) methylphosphonate.

FAB-MS(M+H)$^+$:301.

[0052]

Reference Example 38

A 100 ml THF solution of 2.21 g of diethyl cyano(2-methoxypyridine-4-yl)methylphosphonate was instilled into a 100 ml THF suspension of 0.84 g of lithium aluminum hydride, under ice-cold conditions, and this was stirred for 20 hours at room temperature.

To the reaction solution were successively added, under ice-cold conditions, 0.84 ml of water and 0.84 ml of a 15% aqueous NaOH solution, and after stirring for 30 minutes, a further 2.52 ml of water was added and this was stirred for 2 hours at room temperature. After filtering the reaction solution over Celite and evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (chloroform : MeOH : ammonia water) to produce 510 mg of 2-amino-1-(2-methoxypyridine-4-yl)ethanol.

FAB-MS(M+H)$^+$:169.

[0053]

Reference Example 39

28 ml of a 1.0 M borane-THF complex was added to a 50 ml THF solution of 1.70 g of (2-chloro-6-methoxypyridine-4-yl)acetonitrile under ice cold conditions, and this was stirred for 2 hours at room temperature and for an additional one hour with hot reflux. After cooling the reaction solution, 10 ml of methanol and 12 ml of 6 M hydrochloric acid were successively added, and this was stirred for 30 minutes at room temperature and for an additional 1 hour under heat reflux. A 2M aqueous solution of NaOH was added to the residue produced by evaporating the solvent *in vacuo*, and after extracting this with chloroform, the organic layer was dried with $MgSO_4$. After evaporating the solvent *in vacuo*, the residue was purified by silica gel chromatography (chloroform : MeOH : ammonia water) to produce 740 mg of [2-(2-chloro-6-methoxypyridine-4-yl)ethyl]amine.

FAB-MS$(M+H)^+$:187.

[0054]

Reference Example 40

A mixture of 210 mg of 2-(4-bromo-2,5-diflurophenyl)-4-chloro-6-methylpyrimidine, 200 mg of [2-(2-methoxypyridine-4-yl)ethyl]amine, 454 mg of potassium carbonate and 2 ml of DMI was stirred overnight at 95°C. Water was added to the reaction solution and extracted with toluene, whereafter the organic layer was dried with $MgSO_4$ and the solvent was evaporated *in vacuo* to produce 304 mg of [2-(4-bromo-2,5-diflurophenyl)-6-methylpyrimidine-4-yl][2-(2-methoxy-4-pyridyl)ethyl]amine as an oily yellow substance.

FAB-MS$(M+H)^+$:435,437.

[0055]

Working Example 1

A mixture of 304 mg of [2-(4-bromo-2,5-diflurophenyl)-6-methylpyrimidine-4-yl] [2-(2-methoxy-4-pyridyl)ethyl] amine and 3.0 ml of 48% aqueous hydrogen bromide was stirred overnight at 80°C. A saturated aqueous solution of sodium bicarbonate was added to the reaction solution, and this was extracted with EtOAc, and after washing the organic layer with a 1M aqueous NaOH solution, this was dried with $MgSO_4$. Ether was added to a residue that was produced by evaporating the solvent *in vacuo*, and the deposited solids were collected by filtration to produce 163 mg of 4-(2-{[2-(4-bromo-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one as colorless solids.

[0056]

Working Example 2

0.122 ml of dimethyl sulfate and 1 ml of DMF were added to a mixture of 235 mg of 4-(2-{[2-(4-bromo-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)pyridine-2(1H)-one hydrochloride and 4 ml of a 1M NaOH aqueous solution. After stirring the reaction mixture overnight at room temperature, water was added and the mixture was extracted with ethyl acetate. After washing the organic layer with the saturated aqueous solution of sodium bicarbonate, this

was dried with $MgSO_4$ and filtered. The filtrate was concentrated *in vacuo* to produce a white solid. 10 ml of chloroform-MeOH and 4 ml of a 4M HCl-dioxane solution were added to the substance and this was concentrated *in vacuo*. The residue was crystallized with EtOH-MeOH to produce 180 mg of 4-(2-{[2-(4-chloro-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl)-1-methylpyrimidine-2(1H)-one hydrochloride.

[0057]

Working Example 3

A mixture of 815 mg of 2-(4-bromo-2,5-difluorophenyl)-6-chloro-4-methylpyrimidine, 480 mg of 4-(2-ethylamino)-2(1H)-quinolinone, 3.25 ml of diisopropylethylamine and 20 ml of acetonitrile was stirred overnight at 80°C. The reaction mixture was concentrated *in vacuo* and the residue was purified with silica gel chromatography (chloroform-MeOH) to produce a solid. 1 ml of a 4M dioxane solution of hydrochloric acid was added to this solid in 10 ml of chloroform-MeOH, and this was concentrated *in vacuo* to produce a solid. This solid was washed with ether to produce 260 mg of 4-(2-{[2-(4-bromo-2,5-difluorophenyl)-6-methylpyrimidine-4-yl]amino}ethyl) quinolinone-2(1H)-one hydrochloride.

[0058]

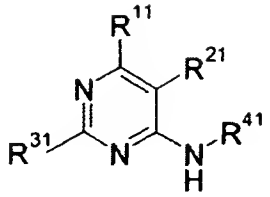
The structures and physical data for the exemplary compounds described above are shown in Table 6. Furthermore, the structures and physical data for exemplary compounds produced by the same preparation methods as used for these exemplary compounds are shown in Tables 6 to 10. Note that, in the tables, the notations have the following meanings.

Ex: Example No.

R^{11}, R^{21}, R^{31} and R^{41}: Substituents in the general formulas (Ph: phenyl, PyO: 2-oxopyridyl, QuiO: 2-oxoquinolinone, di: di, tri: tri). The numerals preceding the substituent denote the site of substitution. Accordingly, for example, 4-Br-2,5-diF-Ph indicates 4-bromo-2,5-difluorophenyl, $-(CH_2)_2$-(1-Me-5-PyO) indicates 1-methyl-2-oxopyridine-5-ylethyl and $-(CH_2)_2$-(4-QuiO) indicates 2-oxo oxoquinolinone -4- ylethyl.)

[0059]

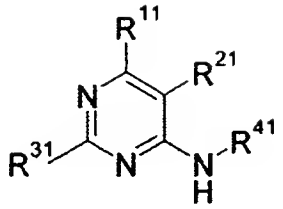
[Table 6]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
1	R^{11} : Me R^{21} : -H R^{31} : 4-Br-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.27(3H,s),2.68(2H,t),3.40-3.60(2H,br),6.09(1H,d),6.15(1H,s),6.31(1H,s),7.26(1H,d),7.40-7.60(1H,br),7.78(1H,dd),7.82-7.91(1H,m),11.3-11.4(1H,br) FMS:421.
2 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Cl-2,5-diF-Ph R^{41} : -$(CH_2)_2$-(1-Me-4-PyO)	NMR:2.45(3H,s),2.74(2H,t),3.37(3H,s),3.60-3.80(2H,m),6.17(1H,d),6.26(1H,s),6.66(1H,s),7.61(1H,d),7.96-8.08(2H,m),9.70(1H,s). FMS:391.
3 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Br-2,5-diF-Ph R^{41} : -$(CH_2)_2$-(4-QuiO)	NMR:2.45(3H,s),3.05-3.20(2H,m),3.75-3.85(2H,m),6.39(1H,s),6.66(1H,m),7.07(1H,t),7.25(1H,d),7.44(1H,t),7.79(1H,dd),7.86(1H,d),8.06(1H,dd),9.69(1H,brs),11.63(1H,brs). FMS:471.
4 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-5-PyO	NMR:2.45(3H,s),2.69(2H,t),3.73(2H,q),6.35(1H,d),6.57(1H,s),7.30-7.36(1H,m),7.50(1H,dd),7.90(2H,d),8.12(2H,d),9.35(1H,s). FMS:385,387.
5 (Ox)	R^{11} : Et R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-5-PyO	NMR:1.21(3H,t),2.52-2.64(4H,m),3.30-3.70(2H,m),6.28(1H,d),6.28(1H,s),7.18(1H,s),7.41(1H,dd),7.42-7.50(1H,m),7.67(2H,d),8.25(2H,d). FMS:399,401.
6 (Ox)	R^{11} : Et R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-(1-Me-5-PyO)	NMR:1.21(3H,t),2.52-2.64(4H,m),3.37(3H,s),3.40-3.70(2H,m),6.29(1H,s),6.34(1H,d),7.39(1H,dd),7.42-7.55(2H,m),7.67(2H,d),8.25(2H,d). FMS:413,415.

[0060]

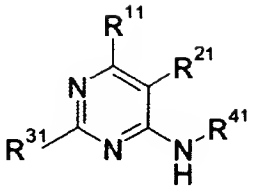
[Table 7]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
7	R^{11} : Et R^{21} : -H R^{31} : 3-Cl-4-F-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:1.22(3H,t),2.58(2H,q),2.72(2H,t),3.40-3.80(2H,br),6.15(1H,dd),6.20(1H,s),6.30(1H,s),7.28(1H,d),7.51(1H,dd),7.40-7.65(1H,br),8.25-8.37(1H,m),8.42(1H,dd). FMS:373.
8	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.26(3H,s),2.68(2H,t),3.30-3.70(2H,br), 6.09(1H,d),6.15(1H,s),6.30(1H,s),7.26(1H,d),7.40-7.55(1H,br),7.55-7.65(1H,m),7.70-8.00(1H,m),11.3-11.4(1H,br) FMS:361.
9	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-5-PyO	NMR:2.26(3H,s),2.58(2H,t),3.40-3.60(2H,m),6.26(1H,d),6.58(1H,brs),7.16(1H,brs),7.37(1H,d),7.46(1H,brs),7.55-7.64(1H,m),7.85-8.00(1H,m),11.39(1H,brs). FMS:361.
10	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -(CH_2)-5-PyO	NMR:2.27(3H,s),4.29(2H,brs),6.31(1H,d),6.34(1H,brs),7.31(1H,s),7.43(1H,dd),7.59(1H,dt),7.75(1H,t),7.90-8.02(1H,m),11.43(1H,brs). FMS:347.
11	R^{11} : Me R^{21} : -H R^{31} : 4-Br-3-F-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.28(3H,s),2.70(2H,t),3.50-3.80(2H,br),6.12(1H,dd),6.18(1H,s),6.30(1H,s),7.27(1H,d),7.36-7.52(1H,br),7.80(1H,dd),8.00-8.02(2H,m),11.1-11.5(1H br) FMS:403.

[0061]

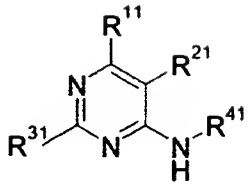
[Table 8]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
12	R^{11} : Me R^{21} : -H R^{31} : 4-Br-3,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.28(3H,s),2.68(2H,t),3.30-3.70(2H,br),6.09(1H,d),6.15(1H,s),6.32(1H,s),7.27(1H,d),7.50-7.65(1H,br),7.78(1H,dd),7.80-7.95(1H,m),11.2-11.7(1H,br) FMS:421.
13 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Cl-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.46(3H,s),2.70-2.90(2H,m),3.67-3.80(2H,m),6.20-6.50(2H,m),6.60-7.05(1H,m),7.35-7.55(1H,m),7.95-8.10(2H,m),9.45-10.00(1H,m). FMS:377.
14 (HCl)	R^{11} : Et R^{21} : -H R^{31} : 4-Cl-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:1.24(3H,t),2.70-2.85(4H,m),3.60-3.80(2H,m),6.20-6.50(2H,m),6.60-6.95(1H,m),7.40-7.55(1H,m),7.95-8.10(2H,m),9.40-10.00(1H,m). FMS:391.
15 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 4-Cl-3,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.50(3H,s),2.70-2.90(2H,m),3.70-3.95(2H,m),6.25-6.55(2H,m),6.55-7.00(1H,m),7.30-7.55(1H,m),8.10-8.40(2H,m),9.10-9.80(1H,m). FMS:377.
16 (HCl)	R^{11} : Et R^{21} : -H R^{31} : 4-Cl-3,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:1.24(3H,t),2.70-3.00(4H,m),3.60-3.95(2H,m),6.35-6.58(2H,m),6.58-6.90(1H,m),7.40-7.60(1H,m),8.15-8.42(2H,m),9.10-9.80(1H,m). FMS:391.
17 (fum)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-(6-Me-4-PyO)	NMR:2.11(3H,s),2.27(3H,s),2.63(2H,t),3.53(2H,br),5.92(1H,s),5.96(1H,s),6.29(1H,br),6.33(1H,s),7.44-7.66(2H,m),7.95(1H,br). FMS:375.

[0062]

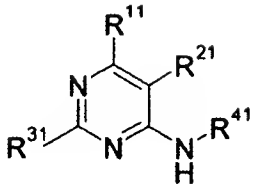
[Table 9]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
18	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-6-Cl-4-PyO)	NMR:2.27(3H,s),2.82(2H,t),3.57(2H,br),6.29(1H,br),6.47(1H,br),6.85(1H,s),7.40-7.65(2H,m),7.94(1H,br),11.30(1H,br). FMS:395.
19	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -(CH_2)-4-PyO	NMR:2.29(3H,s),4.41(2H,br),6.12(1H,d),6.17(1H,s),6.39(1H,br),7.29(1H,d),7.50-7.63(1H,m),7.82-7.97(2H,m),11.40(1H,br). FMS:347.
20 (fum)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_3$-4-PyO	NMR:1.75-1.86(2H,m),2.27(3H,s),2.46(2H,t),3.34(2H,br),6.06(1H,d),6.14(1H,s),6.29(1H,s),6.63(2H,s),7.25(1H,d),7.40-7.63(2H,m),7.82-7.98(1H,m). FMS:375.
21 (fum)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_3$-5-PyO	NMR:1.67-1.80(2H,m),2.26(3H,s),2.38(2H,t),3.25-3.50(2H,m),6.22-6.32(2H,m),6.64(2H,s),7.15(1H,s),7.35(1H,d),7.40-7.50(1H,m),7.55-7.65(1H,m),7.85-8.00(1H,m),12.47(2H,brs). FMS:375.
22 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-6-PyO	NMR:2.44(3H,s),2.84(2H,t),3.75-3.85(2H,m),6.18(1H,d),6.25(1H,d),6.63(1H,s),7.43(1H,dd),7.88-7.96(1H,m),8.00-8.10(1H,m),9.55(1H,s). FMS:361.
23 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -$(CH_2)_2$-(6-HO-4-PyO)	NMR:2.46(3H,s),2.80-2.90(2H,m),3.55-3.82(2H,m),6.02-6.18(1H,m),6.69(1H,s),7.87-8.15(2H,m),9.45-9.70(1H,m). FMS:377.

[0063]

[Table 10]



Ex	R^{11} R^{21} R^{31} R^{41}	Data
24 (HBr)	R^{11} : Me R^{21} : -H R^{31} : 4-Br-Ph R^{41} : -$(CH_2)_2$-3-PyO	NMR:2.45(3H,s),2.74(2H,t),3.73-3.82(2H,m),6.10(1H,t),6.54(1H,s),7.20-7.26(1H,m),7.28-7.34(1H,m),7.89(2H,d),8.17(2H,d),9.40-9.50(1H,brs). FMS:385,387.
25 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -CH_2CH(OH)-4-PyO	NMR:2.46(3H,s),3.35-4.75(7H,m),6.33(1H,d),6.45(1H,s),6.71(1H,s),7.39(1H,d),7.83-8.12(2H,m),9.67(1H,br). FAB-MS:377.
26 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 2,4,5-triF-Ph R^{41} : -CH_2CH(Me)-4-PyO	NMR:1.20(3H,d),2.45(3H,s),2.90-3.08(1H,m),3.45-3.75(2H,m),4.00-5.20(3H,br),6.30-6.42(2H,m),6.69(1H,s),7.41(1H,d),7.84-8.15(2H,m),9.76(1H,br). FAB-MS:375.
27 (HCl)	R^{11} : Me R^{21} : -F R^{31} : 4-Br-2,5-diF-Ph R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.39(3H,d),2.95(2H,t),3.60-3.80(2H,m),6.72(1H,d),6.78(1H,s),7.75(1H,d),7.82-7.94(2H,m),8.00-10.00(3H,m). FAB-MS:439,441.
28 (HCl)	R^{11} : Me R^{21} : -H R^{31} : 6-Br-3-Py R^{41} : -$(CH_2)_2$-4-PyO	NMR:2.50(3H,s),2.70-2.90(2H,m),3.50-3.95(2H,m),6.38(1H,d),6.42(1H,s),6.64(1H,s),7.46(1H,d),7.83(1H,d),8.20-8.75(1H,m),9.10-9.35(1H,m),9.35-9.75(1H,m). FAB-MS:386,388.

[0064]

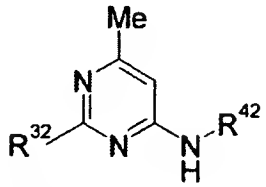
Below, the structures of other compounds of the present invention are shown in Tables 11 to 13. These can easily be prepared using the methods described in the foregoing Preparations and Examples, methods that will be obvious to those skilled in the art, or variations on these methods. Note that, in the tables, the notations have the following meanings.

No.; Compound No.

R^{32}, R^{42}, R^{12} and R^{22}: Substituents in the general formulas (cPr: cyclopropyl, tBu: tertiary butyl).

[0065]

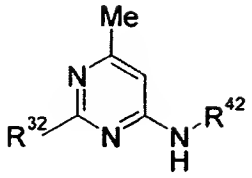
[Table 11]



No	R^{32}	R^{42}
A1	4-Br-2,5-diF-Ph	-CH_2CH(OH)-4-PyO
A2	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-HO_2C-4-PyO)
A3	4-cyano-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A4	4-H_2N-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A5	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-Me-4-PyO)
A6	5-Br-3-Py	-$(CH_2)_2$-4-PyO
A7	4-MeO-Ph	-$(CH_2)_2$-4-PyO
A8	4-O_2N-Ph	-$(CH_2)_2$-4-PyO
A9	4-tBu-Ph	-$(CH_2)_2$-4-PyO
A10	indol-5-yl	-$(CH_2)_2$-4-PyO
A11	5-Br-thiophen-2-yl	-$(CH_2)_2$-4-PyO
A12	4-Br-2,5-diF-Ph	-CH_2CH(Me)-4-PyO
A13	4-Br-2,5-diF-Ph	-$(CH_2)_2$-4-QuiO
A14	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-cyano-4-PyO)
A15	4-HO_2C-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A16	4-H_2NOCHN-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A17	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(3-Me-4-PyO)
A18	4-F_3C-Ph	-$(CH_2)_2$-4-PyO
A19	4-Ph-Ph	-$(CH_2)_2$-4-PyO
A20	benzodioxol-5-yl	-$(CH_2)_2$-4-PyO
A21	4-HO-Ph	-$(CH_2)_2$-4-PyO
A22	benzofuran-5-yl	-$(CH_2)_2$-4-PyO
A23	1-Me-benzimidazol-5-yl	-$(CH_2)_2$-4-PyO
A24	4-Br-2,5-diF-Ph	-CH(Me)CH_2-4-PyO
A25	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(6-EtO_2C-4-PyO)

[0066]

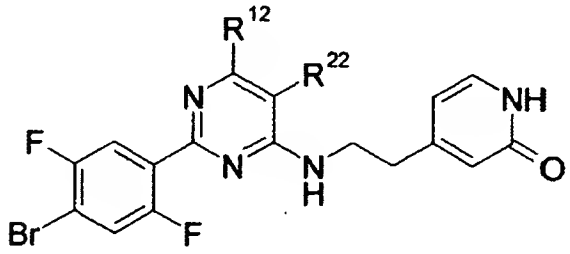
[Table 12]



No	R^{32}	R^{42}
A26	4-EtO_2C-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A27	4-(EtO_2C)HN-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A28	4-Br-2,5-diF-Ph	-$(CH_2)_2$-(5-Me-4-PyO)
A29	6-Cl-3-Py	-$(CH_2)_2$-4-PyO
A30	4-Me_2N-Ph	-$(CH_2)_2$-4-PyO
A31	4-F_3CO-Ph	-$(CH_2)_2$-4-PyO
A32	4-Me-Ph	-$(CH_2)_2$-4-PyO
A33	4-(Me_2N)O_2S-Ph	-$(CH_2)_2$-4-PyO
A34	benzothiophen-5-yl	-$(CH_2)_2$-4-PyO
A35	4-H_2NOC-2,5-diF-Ph	-$(CH_2)_2$-4-PyO
A36	4-Br-2,5-diF-Ph	-$(CH_2)_2$-1-PyO

[0067]

[Table 13]



No	R^{12}	R^{22}
A36	Et	Me
A37	Me	Me
A38	cPr	H
A39	Et	F